IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:

Inventors:	Carsten Momma, Andreas Becker, Robert Schmiedl, and Bernd Heublien
Serial No.:	10/630,355
Filed:	July 30, 2003
For:	ENDOVASCULAR IMPLANT FOR THE INJECTION OF AN ACTIVE SUBSTANCE INTO THE MEDIA OF A BLOOD VESSEL
Art Unit:	3738
Examiner:	Brian E. Pellegrino

BRIEF ON APPEAL

To: Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal under 37 C.F.R. §1.191 to the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office from the final rejection of claims 1, 3-15, and 26-29 in the above-identified patent application. One (1) copy of Appellant's Brief on Appeal is filed herewith, and the requisite filing fee under 37 C.F.R. §1.17(f) is also paid herewith.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest in the present application is Biotronik Mess- und Therapiegeraete GmbH & Co., by assignment from inventors Carsten Momma, Andreas Becker, Robert Schmiedl, and Bernd Heublien. The assignment is recorded in the United States Patent and Trademark Office at Reel 014916, Frame 0391.

II. RELATED APPEALS AND INTERFERENCES

There has been no previous appeals in this application.

There have been no interferences or related litigation.

III. STATUS OF CLAIMS

The status of the claims in this application is:

1. TOTAL NUMBER OF CLAIMS IN APPLICATION

There are 18 pending claims in this application, numbered 1, 3-15, and 26-29.

In the Office Action of March 4, 2005, the Examiner stated that the application contained claims directed to three patentably distinct inventions: Invention I: Claims 1-29, classified in class 623, subclass 1.42; Invention II: Claims 30 and 31, classified in class 427, subclass 534; Invention III: claim 32, classified in class 430, subclass 281.1. The Examiner also indicated that the application contained claims directed to six patentably distinct species as follows:

Species A: Fig. 2
Species B: Fig. 3
Species C: Fig. 4
Species D: Fig. 5
Species E: Fig. 6
Species F: Fig. 7.

The Appellant elected Invention I, Species A with traverse. Claims 16-25 and 30-31 were withdrawn from consideration.

In the Amendment mailed March 29, 2006, the Appellant cancelled claims 2 and 30-32.

With regard to the claims on appeal, claims 1, 3-11, 14, 15 and 26-29 are generic, and claims 12 and 13 are directed to Species A (Fig. 2).

2. STATUS OF ALL OF THE CLAIMS

A. Claims canceled: 2, and 30-32.

B. Claims withdrawn from consideration but not canceled: 16-25.

C. Claims pending: Claims 1, 3-29.

D. Claims allowed: NONE.

E. Claims rejected: 1, 3-15, 26-29.

3. CLAIMS ON APPEAL

The claims on appeal are claims 1, 3-15, 26-29.

IV. STATUS OF AMENDMENTS

No Amendments have been filed subsequent to the Final Action of November 16, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

All citations to the specification refer to the specification that was filed on July 30, 2003. FIGS. 1 and 2 of the present application are reproduced below.

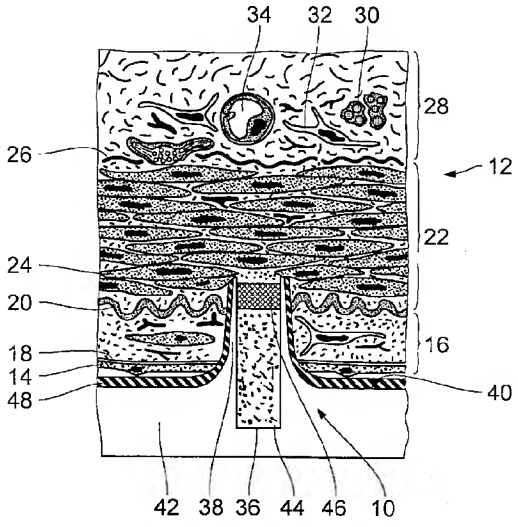

Fig. 1

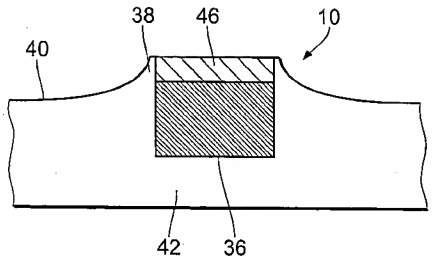

Fig. 2

Independent claim 1 is directed to an endovascular implant for applying an active substance **36** into the media **22** of a blood vessel **12**. (Paragraph 0012, Fig. 1). The implant comprises a base body **42** which has a plurality of microdevices **10** for applying the active substance **36**, disposed at least in a portion of the surface **40** of the implant, the microdevices **10** being adapted to face towards the blood vessel **12**. (Paragraphs 0033-0040, particularly 0036-0038, Abstract, Fig.1). Each microdevice **10** includes at least one microcannula **38** which projects from the implant surface **40** by between 100 and about 400 μm such that, when the implant bears in surface contact against a wall **14** of the blood vessel **12**, the microcannula **38** penetrates into the media **22** of the blood vessel **12**. (Paragraphs 0014 and 0036, Fig. 1). At least

one deposit of the active substance **36** is in communication with at least one microcannula **10**. (Paragraph 0039, Fig. 1).

Claim 3 recites that the at least one microcannula **10** projects from the implant surface **40** by between about 150 and about 300 μm and claim 4 recites that the at least one microcannula **10** projects from the implant surface **40** by between about 180 and about 250 μm. Claim 5 recites that the at least one microcannula **10** has a diameter of 20-200 μm. (Paragraph 0036).

Claims 6 and 7 recite that the microdevices **10** are component parts of the base body **42**. (Paragraph 0016). Claims 8 and 9 recite that the microdevices **10** are applied to the base body **42** using hybrid technology. (Paragraph 0017). Claims 10 and 11 recite that the at least one active substance **36** is liberated only after penetration of the at least one microcannula **38** into the media **22** of the blood vessel **12**. (Paragraph 0018).

Claims 12 and 13 recite that the implant includes a cover layer **46** of a biodegradable material that closes the plurality of microdevices **10** after the at least one active substance **44** has been introduced into the active substance deposit **36**. (Paragraphs 0018 and 0039). Claims 14 and 15 recite that the at least one active substance **44** is embedded in a biodegradable drug carrier. (Paragraph 0018).

Claims 16 and 17 recite that a plurality of active substances are introduced into the active substance deposit such that stepwise liberation of the active substances occurs. Claims 18 and 19 recite that a plurality of layers of biodegradable drug carriers with embedded active substances are introduced into the active substance deposit and are successively broken down. Claims 20 and 21 recite the presence of at least one separating layer of a biodegradable material, each of which is successively broken down and which separates the various active substances from each other. (Paragraph 0019).

Claim 22 recites that regions of the surface of the implant that are outside the microdevice are covered with a layer of a biodegradable material. (Paragraph 0020).

Claim 23 depends from claim 22 and recites that this layer of biodegradable material terminates flush in a peripheral direction at a tip of the microcannulae of the microdevice or completely covers the microdevice and a breakdown behaviour on the part of the layer is matched with the liberation behaviour of the active substance, such that liberation of the active substance begins only after complete breakdown of the layer. Claim 24 recites the presence of self-expanding structures which promote progressive penetration of the microcannulae into the vessel wall. Claim 25 recites that the layer of biodegradable material comprises hyaluronic acid polymers with different degradation kinetics. (Paragraph 0021).

Claim 26 recites that the implant is a stent and claim 27 recites that the stent is adapted for use as a coronary stent. (Paragraph 0022).

Claim 28 recites that the base body is formed at least in portion-wise manner from a biodegradable material. Claim 29 recites that the base body is formed, at least in portion-wise manner, from a magnesium alloy. (Paragraph 0023).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 1, 3-12, and 26-29 are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Pat. No. 6,254,632 to Wu et al.

2. Whether claims 14 and 15 are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Pat. No. 6,254,632 to Wu et al. in view of U.S. Pat. No. 6,287,628 to Hossainy et al.

VII. ARGUMENTS

1. The Rejection of Record

Currently, claims 1 and 3-29 are pending in the present application. Claims 16-25 have been withdrawn from consideration. Claims 1, 3-15 and 26-29 stand rejected.

In the Office Action of November 16, 2006, the Examiner rejected claims 1, 3-13 and 26-29 as being obvious in view of U.S. Pat. No. 6,254,632 to Wu et al. (hereinafter "Wu"). The Examiner maintains that Wu discloses "a stent having a base body with a plurality (col. 8, lines 50-56) of microdevices 200 that project from the implant surface to form a microcannula 218 on the outer surface to engage a vessel wall (col. 6, lines 13-17)." The Examiner also maintained that the recitation in the claims that the microcannulae penetrate into the media of the blood vessel was given no weight. The Examiner further inferred the length of the microcannulae of Wu from the description of cover surrounding the stent (Wu, column 9, lines 17-19).

The Examiner also rejected claims 14 and 15 as obvious over Wu in view of U.S. Pat. No. 6,287,628 to Hossainy et al. (hereinafter "Hossainy"). The Examiner asserts that Wu teaches the elements of these claims except the use of a biodegrable drug carrier to hold the active substance, and that Hossainy provides such a teaching.

Figs. 2A-2C of Wu are reproduced below.

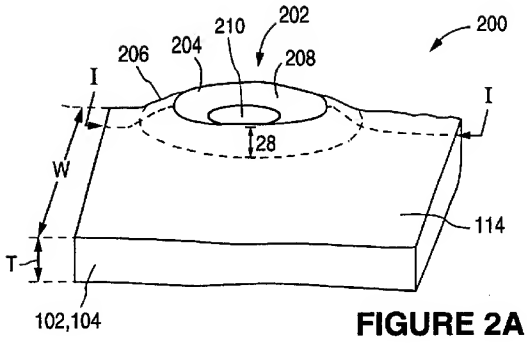

FIGURE 2A

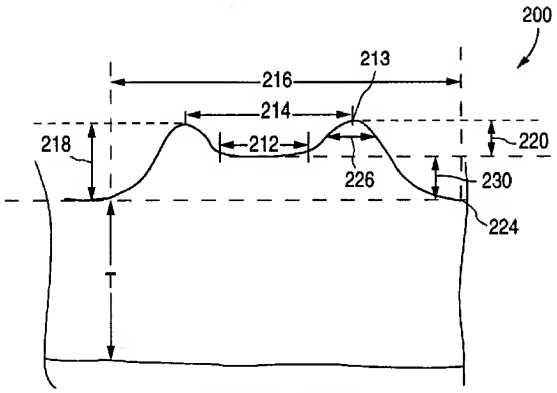

FIGURE 2C

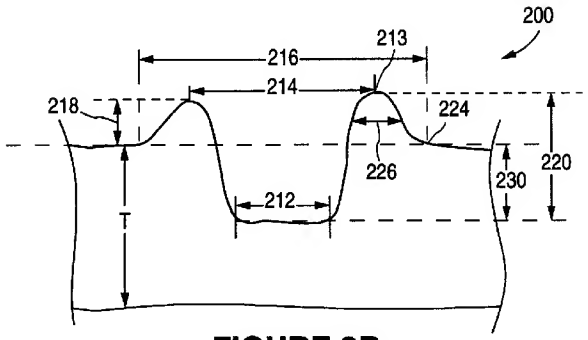

FIGURE 2B

2. Claims Rejections under 35 U.S.C. §103(a)

A claimed invention is unpatentable under 35 U.S.C. §103 if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. 35 U.S.C. § 103 (1994); *Graham v. John Deere Co.,* 383 U.S. 1, 14 (1966); *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ , No. 04-1350, *slip op.* at 2 (2007). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18; *KSR Int'l* at 2.

A. The Examiner has the Burden to Establish a Prima Facie Case of Obviousness

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness. MPEP §2142. If the Examiner does not establish a *prima facie* case, the applicant is under no obligation to respond. MPEP §2142. To reach a proper determination under §103, the Examiner must step backward in time and into the shoes of the hypothetical person of ordinary skill in the art when the invention was unknown and just before it was made. MPEP §2142. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. MPEP §2142.

B. Criteria/Analysis the Examiner Must Meet to Establish a Prima Facie Case of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met by the Examiner.

1. Motivation to Combine

First, there must be some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998).

Under Federal Circuit precedent, the showing of a motivation to combine or modify prior art must be clear and particular, and broad conclusory statements about the teachings of one or more references, standing alone, are not "evidence." *In re Dembiczak*, 175 F.3d 994, 1000, 50

U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Further, the showing of obviousness "requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references." *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617.

Ultimately, this first criterion provides "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis." *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. This is because "most if not all inventions arise from a combination of old elements," potentially allowing every element of the claimed invention to be found in the prior art. *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). Solely identifying each element of the claimed invention in the prior art is not enough to defeat patentability of the invention as a whole, unless there existed a teaching, suggestion, or motivation to combine the prior art references. *Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Otherwise, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *Rouffet,* 149 F.3d at 1357, 47 U.S.P.Q.2d at 1457. Thus, the initial burden is on the examiner to establish the existence of a teaching, suggestion, or motivation to combine the prior art references at the time the invention was made.

Recently, the Supreme Court rejected the use of the "teaching, suggestion, or motivation" test (TSM test) as a "rigid and mandatory (formula)" that "limits the obviousness inquiry" in favor of viewing the TSM test as a "general principle" and a "helpful insight." *KSR Int'l Co.* at

15. However, the Supreme Court also reiterated, that an invention is not shown to be obvious "merely by demonstrasting that each of its elements was, independently, known in the prior art." *KSR Int'l Co.* at 14. Furthermore, the Supreme Court did not eliminate the motivation to combine from an obviousness analysis. To the contrary, the Court indicated, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR Int'l* at 15. Therefore, while the Supreme Court's decision in *KSR International Co.* expands the possible sources of motivation to combine, it does not eliminate the requirement.

2. Reasonable Expectation of Success

Second, there must be a reasonable expectation of success. Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

3. Prior Art Must Teach or Suggest All the Claim Limitations.

The third and final requirement for a finding of obviousness requires the prior art reference (or references when combined) to teach or suggest all the claim limitations. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (COCA 1970).

C. Argument Regarding Claim 1 And All Pending Claims As Dependent Upon Claim 1

1. U.S. Patent No. 6,254,652 to Wu Does Not Teach Or Suggest All Elements Of Claim 1

The present invention is directed to an endovascular implant adapted to deliver and active substance to the media of a blood vessel in which it is placed. This is accomplished by microstructures designed to penetrate past the blood vessel and into the media of the blood vessel. This represents an improvement over the prior art, which provides active substances that are applied only to the intima of a blood vessel (See Paragraph 0010). Diffusion from the prior implants into the blood vessel wall however, is impeded by plaque, calcification or thickened vessel wall layers. (Paragraph 0010).

The Examiner maintains that Wu discloses "a stent having a base body with a plurality (col. 8, lines 50-56) of microdevices 200 that project from the implant surface to form a microcannula 218 on the outer surface to engage a vessel wall (col. 6, lines 13-17)." The Examiner also maintains that the description of the cover of the stent of Wu could also support the interpretation of the structures of Wu having the same length as the microcannulae of the present invention. However, the Examiner's inference is only one of several possible inferences and the use of the thickness of a cover on Wu's stent to infer the length of the microcannulae is contradicted by the explicit statements of Wu regarding the length of the microdevices. As previously stated in the response filed September 8, 2006 (page 8), Wu clearly discloses a lip height 218 of 10-80 μm (Wu, col. 11, lines 65-67, Figs. 2B-2C).

While Wu provides a stent that includes structures that allow delivery of a therapeutic substance directly to the wall of the vessel, Wu does not teach or suggest microcannulae that

penetrate into the vessel wall to the media of the vessel. Wu only teaches that the microcannulae, or "craters" as termed by Wu, "can be used to deliver therapeutic substances from the stent directly to the lumen wall..." (column 2, lines 60-62). As shown in Fig. 1 and as explained in the accompanying description in paragraph 0034 of the present application, the wall of an artery contains three layers: the intima 16 which is bounded by an inner elastic membrane 20 and a basal lamina 18 underlying endothelium cells 14; the media 22; and the adventitia 28. Wu merely provides that the protruding structures or craters "engage the lumen of the passageway ... to help prevent the stent from slipping out of the treatment site." (Wu, Column 6, lines 15-17). As stated in the response of February 27, 2006, a "lumen" is actually an inner open space or cavity, in this case, of the blood vessel. Therefore, by using this terminology, Wu can only mean that the craters 200 contact ("engage") the wall of the blood vessel at its inner surface. Wu does not teach or suggest structures that penetrate into the vessel past the endothelium, the basal lamina, and the inner elastic membrane and allow delivery of such substances directly into the media. Additionally, Wu's terminology (i.e. "craters") for these structures further indicates that Wu does not intend or envision these structures as delivering an active substance to the media of a blood vessel as in the present invention. Rather, the structures of Wu are merely intended to engage and secure the stent to a vessel or to a cover for the stent.

The Examiner contends that the Applicant's assertion that Wu's stent would not penetrate to the media, "is an improper statement because the Applicant has arbitrarily selected a dimension less than what Applicant's claims recite." This is clearly not true. The specification goes to great lengths to explain the benefits and close tolerances necessary to deliver an active substance to the media of a blood vessel. (See paragraphs 0014 and 0036). On the other hand, the disclosure of the length of the lip height 218 of Wu, 10-80 μm is also clear. No other lip

height is disclosed by Wu. In fact, it is the Examiner's selection one one possible inference of the lip height of Wu, taken from the description of the cover of Wu, that has been arbitrarily selected to match the claimed microcannulae length. Therefore, the Examiner's finding of a possible suggestion of the claimed invention in Wu is based on hindsight. The Examiner also cites *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-1383 (Fed Cir 2003) as supporting the rejection. However, *Peterson* involved the obviousness of a range that was encompassed by a larger prior disclosed range, not a range adjacent to a prior disclosed range as in the present application.

2. There Is No Motivation To Modify The Stent Of Wu To Arrive At The Present Invention.

One of ordinary skill in the art would not have found any suggestion or motivation to modify the length of the "craters" of Wu to 100-400 μm, or to any length other than that disclosed by Wu, 10-80 μm. The Examiner states that the intended use of the microcannulae in the claims carries no weight absent a distinguishing structure. However, such a structure is explicitly provided by the claims by indicating the length necessary to perform the function. Contrary to the Examiner's assertions, the Applicants have provided a distinct advantage of the claimed microcannula length ranges, namely, to deliver therapeutic products directly into the media of blood vessels, not just to the interior surface of the blood vessels. Wu does not provide any teaching or suggestion that such delivery is desirable or possible. Neither has the Examiner provided any indication that such a motivation to modify Wu would be found by one of ordinary skill in the art in the knowledge generally available to one of skill in the art. In fact, as discussed in the specification, and as well known in the art, insult to the walls of a blood vessel, including insult occurring as a result of stent placement, can cause restenosis. (See Paragraph 0035)

Therefore, one of skill in the art would not have found any motivation in Wu or in the knowledge generally available to one of ordinary skill in the art, to modify an implant such as a stent provided by Wu to actually penetrates the walls of a blood vessel. Furthermore, some claims provide further elements designed to overcome any residual tendency to cause restenosis from penetration of the blood vessel wall, particularly claims 24 and 25 (see Paragraph 0021).

3. There Is No Reasonable Expectation Of Success In Modifying The Length Of The Microstructures Of Wu

One of ordinary skill in the art would likelwsie have no expectation of success in modifying Wu. As stated above, restenosis was a well recognized problem associated with stent usage. It was also recognized that injury to the blood vessel wall could cause restenosis. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in treating patients successfully with a stent that included structures that actually penetrated the blood vessel wall prior to the present invention.

D. Argument Regarding Claims 14 and 15

The Examiner asserts that Wu fails to disclose the use of a biodegrable drug carrier to hold the active substance, and that Hossainy provides such a teaching. However, neither Wu nor Hossainy teach or suggest microcannulae as recited in the claims, as provided above. The arguments provided with regard to Wu are repeated herein with regard to claims 14 and 15. The examiner has provided no allegation that Hossainy provides a teaching or suggestion of such microcannulae.

E. Conclusion

The Applicants respectfully assert that all the pending claims are allowable for at least the following reasons: and this claim and all those pending claims which depend from it patentably distinguish over Wu.

1. Wu does not teach or suggest all the elements of claim 1, from which the remaining pending claims depend.
2. There is no motivation to modify the microstructures of Wu to provide microcannulae that deliver an active substance to the media of a blood vessel.
3. There is no reasonable expectation of success in the microstructures of Wu to provide microcannulae that deliver an active substance to the media of a blood vessel

In accordance with the foregoing, the Applicants respectfully request reversal of the Examiner and allowance of all claims.

Respectfully submitted,

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_____

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VIII. APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

1. An endovascular implant for applying an active substance into the media of a blood vessel, said implant comprising:

a base body which has a plurality of microdevices for applying the active substance disposed at least in portion-wise manner at a surface of the implant adapted for facing towards the blood vessel, wherein each said microdevice includes at least one microcannula which projects from the implant surface by between 100 and about 400 μm such that, when the implant bears in surface contact against a wall of the blood vessel, the microcannula penetrates into the media of the blood vessel, and

at least one deposit of the active substance which is in communication with at least one said microcannula.

3. The implant of claim 2, wherein:

the at least one microcannula projects from the implant surface by between about 150 and about 300 μm.

4. The implant of claim 3, wherein:

the at least one microcannula projects from the implant surface by between about 180 and about 250 μm.

5. The implant of claim 2, wherein:

the at least one microcannula are of a diameter of 20 - 200 μm.

6. The implant of claim 1, wherein:

the microdevices are component parts of the base body.

7. The implant of claim 5, wherein:

the microdevices are component parts of the base body.

8. The implant of claim 5, wherein:
the microdevices are applied to the base body using hybrid technology.

9. The implant of claim 1, wherein:
the microdevices are applied to the base body using hybrid technology.

10. The implant of claim 5, wherein:
a liberation behaviour in respect of the at least one active substance to be deposited is so established that the at least one active substance is liberated only after penetration of the at least one microcannula into the media of the blood vessel.

11. The implant of claim 1, wherein:
the at least one active substance to be deposited is liberated only after penetration of the at least one microcannula into the media of the blood vessel.

12. The implant of claim 10, wherein:
a cover layer of a biodegradable material closes the plurality of microdevices after the at least one active substance has been introduced into the active substance deposit.

13. The implant of claim 11, wherein:
a cover layer of a biodegradable material closes the plurality of microdevices after the at least one active substance has been introduced into the active substance deposit.

14. The implant of claim 10, wherein:
the at least one active substance is embedded in a biodegradable drug carrier.

15. The implant of claim 11, wherein:
the at least one active substance is embedded in a biodegradable drug carrier.

16. (withdrawn) The implant of claim 10, wherein:

a plurality of active substances are introduced into the active substance deposit such that stepwise liberation of the active substances occurs.

17. (withdrawn) The implant of claim 11, wherein:

a plurality of active substances are introduced into the active substance deposit such that stepwise liberation of the active substances occurs.

18. (withdrawn) The implant of claim 16, wherein:

a plurality of layers of biodegradable drug carriers with embedded active substances are introduced into the active substance deposit and are successively broken down.

19. (withdrawn) The implant of claim 17, wherein:

a plurality of layers of biodegradable drug carriers with embedded active substances are introduced into the active substance deposit and are successively broken down.

20. (withdrawn) The implant of claim 16, comprising:

at least one separating layer of a biodegradable material, each of which is successively broken down and which separates the various active substances from each other.

21. (withdrawn) The implant of claim 17, comprising:

at least one separating layer of a biodegradable material, each of which is successively broken down and which separates the various active substances from each other.

22. (withdrawn) The implant of claim 1, wherein:

regions of the surface of the implant that are outside the microdevice are covered with a layer of a biodegradable material.

23. (withdrawn) The implant of claim 22, wherein:

the layer of biodegradable material terminates flush in a peripheral direction at a tip of the microcannulae of the microdevice or completely covers the microdevice and

a breakdown behaviour on the part of the layer is matched with the liberation behaviour of the active substance, such that liberation of the active substance begins only after complete breakdown of the layer.

24. (withdrawn) The implant of claim 22, comprising:

self-expanding structures which promote progressive penetration of the microcannulae into the vessel wall.

25. (withdrawn) The implant of claim 22, wherein:

the layer of biodegradable material comprises hyaluronic acid polymers with different degradation kinetics.

26. (original) The implant of claim 1, wherein:

the implant is a stent.

27. The implant of claim 26, wherein:

the stent is adapted for use as a coronary stent.

28. The implant of claim 26, wherein:

the base body is formed at least in portion-wise manner from a biodegradable material.

29. The implant of claim 28, wherein:

the base body is formed, at least in portion-wise manner, from a -magnesium alloy.

IX. EVIDENCE APPENDIX

EXHIBIT 1
Office Action dated November 16, 2006

EXHIBIT 2

U.S. Patent No. 6,254, 632 to Wu

Submitted by Applicant in an Information Disclosure Statement filed January 21, 2004.

First Reviewed by the Examiner June 6, 2005.

First Cited by the Examiner in an Office Action June 8, 2005.

EXHIBIT 3

U.S. Patent No. 6,287,628 to Hossainy

Submitted by Applicant in an Information Disclosure Statement filed January 21, 2004.

First Reviewed by the Examiner June 6, 2005.

First Cited by the Examiner in an Office Action June 8, 2005.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,355	07/30/2003	Carsten Momma	117163.00077	9258

21324 7590 11/16/2006

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EXAMINER	
PELLEGRINO, BRIAN E	

ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,355	MOMMA ET AL.	
	Examiner	Art Unit	
	Brian E Pellegrino	3738	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-29* is/are pending in the application.

4a) Of the above claim(s) *16-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1,3-13,26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (6254632). Wu et al. disclose (Fig. 2B) a stent having a base body with a plurality (col. 8, lines 50-56) of microdevices **200** that project from the implant surface to form a microcannula **218** on the outer surface to engage the vessel wall, col. 6, lines 13-17. Please note the intended use of the "microcannulae" to "penetrate into the media of the blood vessel" carries no weight in the absence of any distinguishing structure. Wu also discloses the thickness of the cover is from 25-500μm, col. 9, lines 13,14. Wu additionally discloses that the protrusions or "microcannulae" can extend out of the cover, col. 9, lines 17-19. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have a height of a protrusion or "micorcannulae dimension that falls within the claimed range of 100 to about 400μm since it would need to have a dimension as such in order to protrude through the cover having the thickness range between if it were 300 to 500μm as disclosed by Wu, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. Fig. 4A shows a cover layer **420** of biodegradable material (col. 6, lines 33-42) that closes the active substance **410** in the deposit. The microdevices are fully capable of being applied using hybrid technology. Wu additionally discloses the active substance

is liberated once the stent is implanted and the microcannulae engage the vessel wall, col. 6,lines 18-26. Wu discloses the stent can be made from a biodegradable material and from a magnesium alloy, col. 4, lines 43,44,47,48,54.

With respect to claims 3,4 Wu does disclose the lengths or depths of the microcannulae can be any dimension depending on the amount of drug desired to be delivered, col. 6, lines 61-66. However, Wu fails to disclose the lengths of the microcannulae to be 180μm-250μm. It would have been an obvious matter of design choice to modify the length of the microcannulae, since applicant has not disclosed that using a length of 150μm or 180μm provides any advantage, or solves a stated problem, or is used for any particular purpose. One of ordinary skill in the art, furthermore, would have expected Applicant's invention to perform equally well with the length taught by Wu et al. or the claimed lengths in claim(s) 3,4 because both stents perform the same function of delivering a therapeutic substance to a vessel and anchoring the stent in the wall.

Claims 14,15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. '632 in view of Hossainy et al. (6287628). Wu et al. is explained supra. However, Wu fails to disclose the use of a biodegradable drug carrier to hold the active substance. Hossainy et al. teach that impregnated polymers can be used to hold therapeutic materials to place in the microcannulae (col. 9, lines 21-25) and that biodegradable carriers can be used, col. 10,lines 50-52,57-59. It would have been obvious to one of ordinary skill in the art to use a biodegradable carrier to hold the drug

and fill the microcannulae as taught by Hossainy in the stent of Wu et al. such that it degrades over time and has a controlled release rate at the implantation site.

Response to Arguments

Applicant's arguments filed 9/8/06 have been fully considered but they are not persuasive. In response to applicant's argument that Wu's protrusions on the stent cannot penetrate the media of a blood vessel, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Wu clearly discloses "microcannulae" as claimed and Applicant has failed to distinguish any structural feature. Applicant states the protrusion of Wu's stent has dimensions that would not penetrate the media. However, this is an improper statement because the Applicant arbitrarily selected a dimension less than what Applicant's claims recite. MPEP 2144.05 states a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian E Pellegrino whose telephone number is 571-272-4756. The examiner can normally be reached on M-Th (6:30am-4pm) and alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached at 571-272-4754. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BRIAN E. PELLEGRINO
PRIMARY EXAMINER

US006254632B1

(12) **United States Patent**
Wu et al.

(10) **Patent No.: US 6,254,632 B1**
(45) **Date of Patent: Jul. 3, 2001**

(54) **IMPLANTABLE MEDICAL DEVICE HAVING PROTRUDING SURFACE STRUCTURES FOR DRUG DELIVERY AND COVER ATTACHMENT**

(75) Inventors: **Steven Z. Wu**, Santa Clara; **Sameer Harish**, Fremont; **Deborra Sanders-Millare**; **Judy A. Guruwaiya**, both of San Jose, all of CA (US)

(73) Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/675,044**

(22) Filed: **Sep. 28, 2000**

(51) **Int. Cl.**[7] **A61F 2/06**
(52) **U.S. Cl.** **623/1.15**
(58) **Field of Search** 623/1.13, 1.15, 623/1.16, 1.44, 1.34, 1.1, 1.42, 1.12, 1.11

(56) **References Cited**

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6,190,404	*	2/2001	Palmaz et al.	623/1

FOREIGN PATENT DOCUMENTS

WO 98/23228	6/1998	(WO)	A61F/2/06

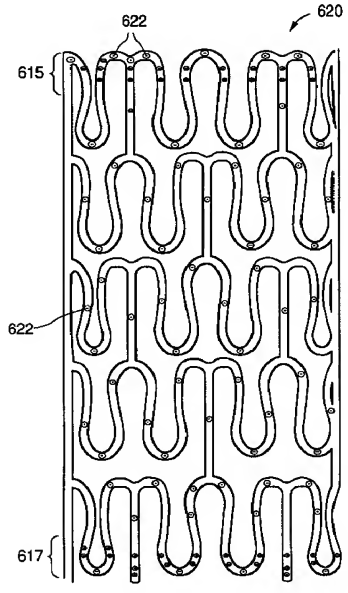
* cited by examiner

Primary Examiner—Henry J. Recla
Assistant Examiner—(Jackie) Tan-Uyen T. Ho
(74) *Attorney, Agent, or Firm*—Skjerven Morrill MacPherson LLP; James E. Parsons; Signe M. Holmbeck

(57) **ABSTRACT**

A method for forming an implantable medical device, such as a stent, covered stent, or synthetic stent graft, is provided. Protruding structures are formed on a surface of the device. The protruding structures have a central depression region surrounded by a lip. The protruding structures can have a variety of shapes, including circular and ovular shapes, or the protruding structure can form a groove. The protruding structures can be used to engage a cover. Glue can be added to the protruding structures to help secure the cover. The protruding structures can also contain a therapeutic substance or substances for release in situ. The protruding structures can be formed using a laser discharge to create a hole in the stent surface followed by directing a pressurized stream of grit at the surface.

31 Claims, 8 Drawing Sheets



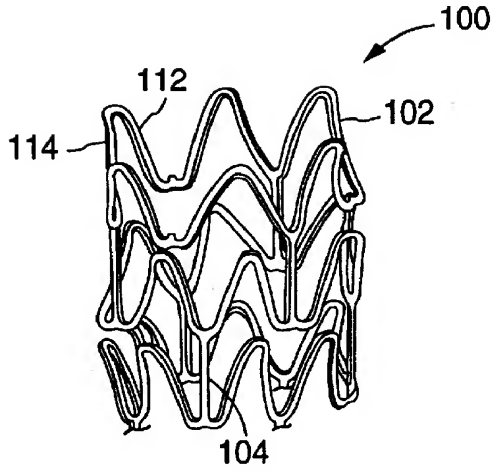


FIGURE 1
(PRIOR ART)

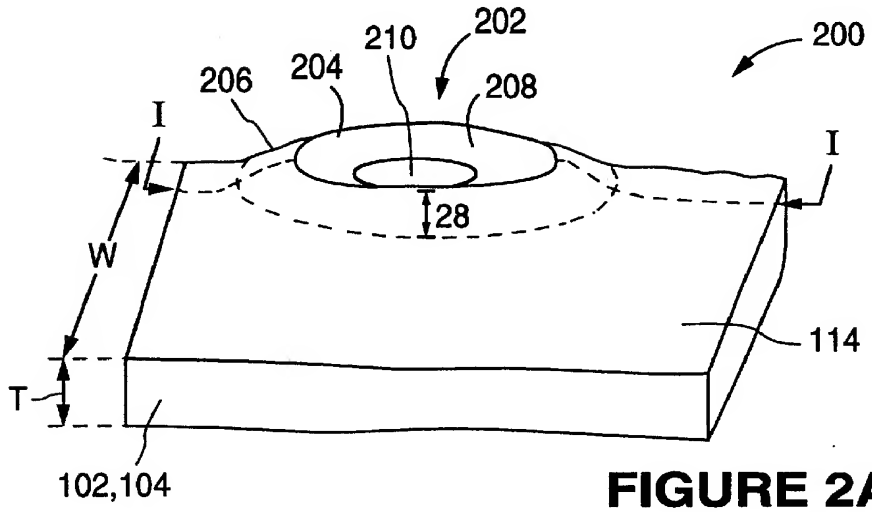


FIGURE 2A

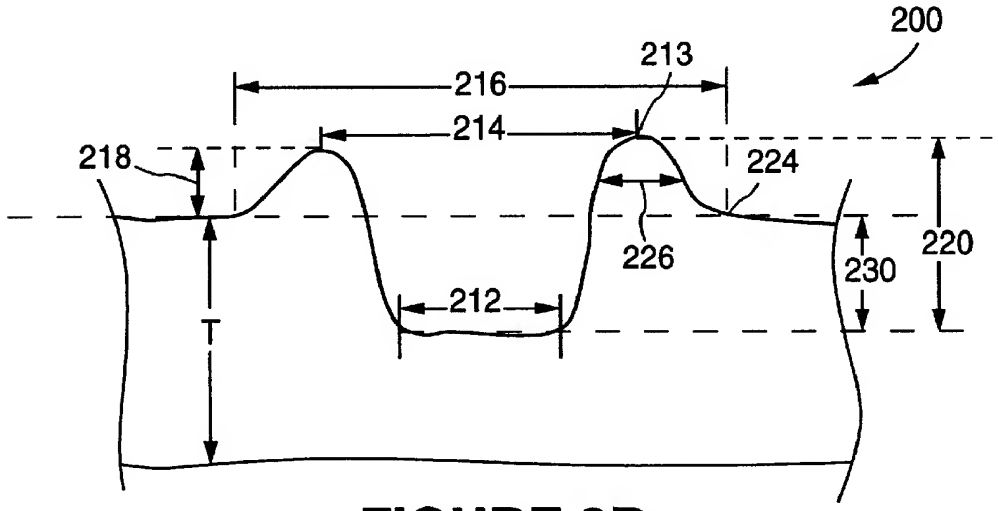


FIGURE 2B

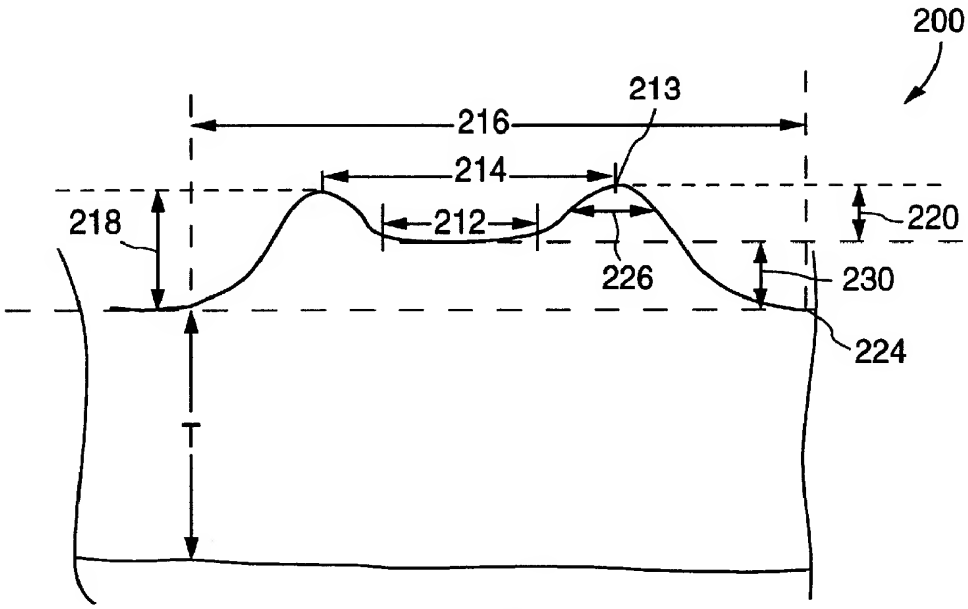


FIGURE 2C

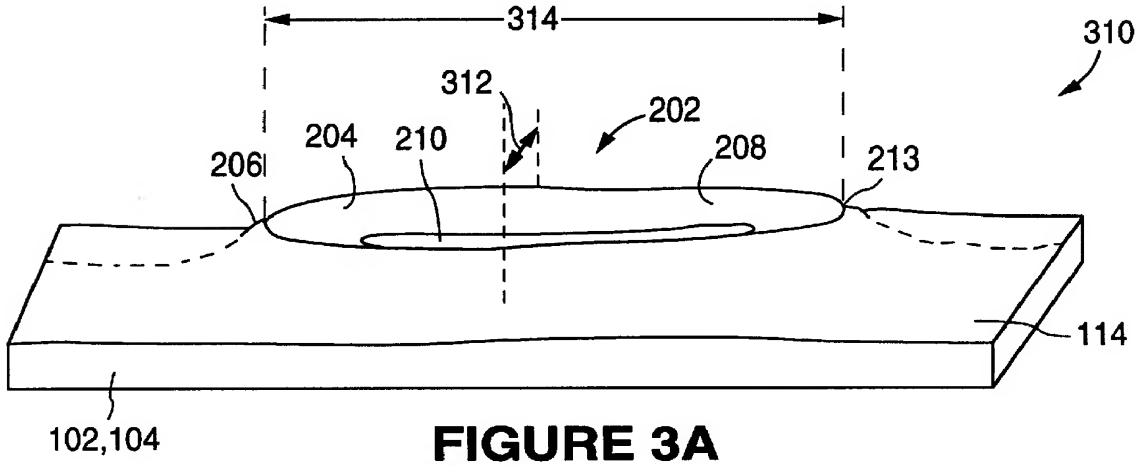


FIGURE 3A

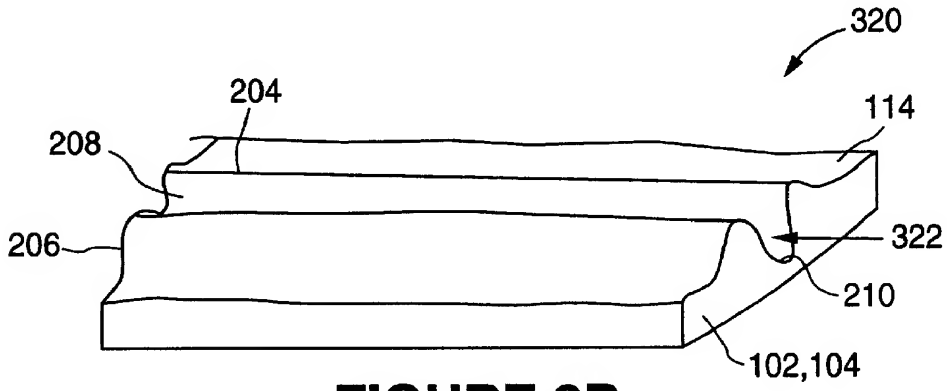


FIGURE 3B

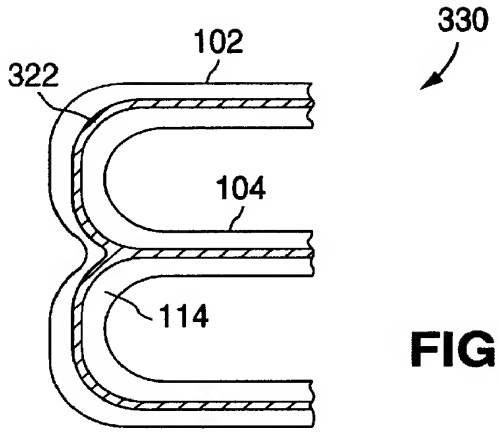


FIGURE 3C

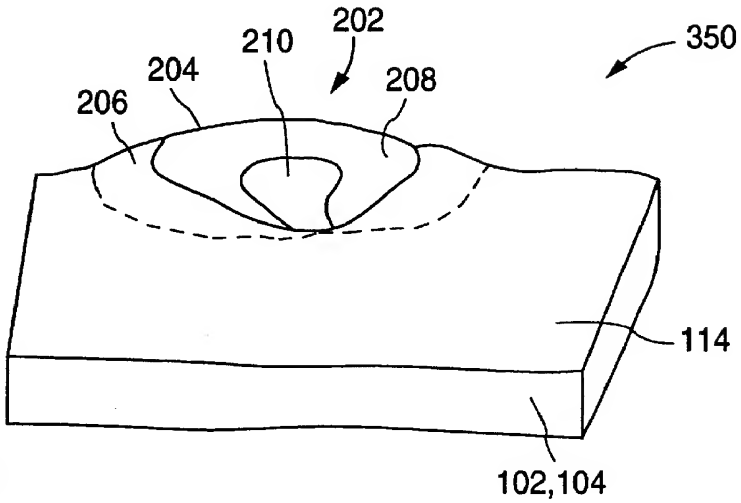


FIGURE 3D

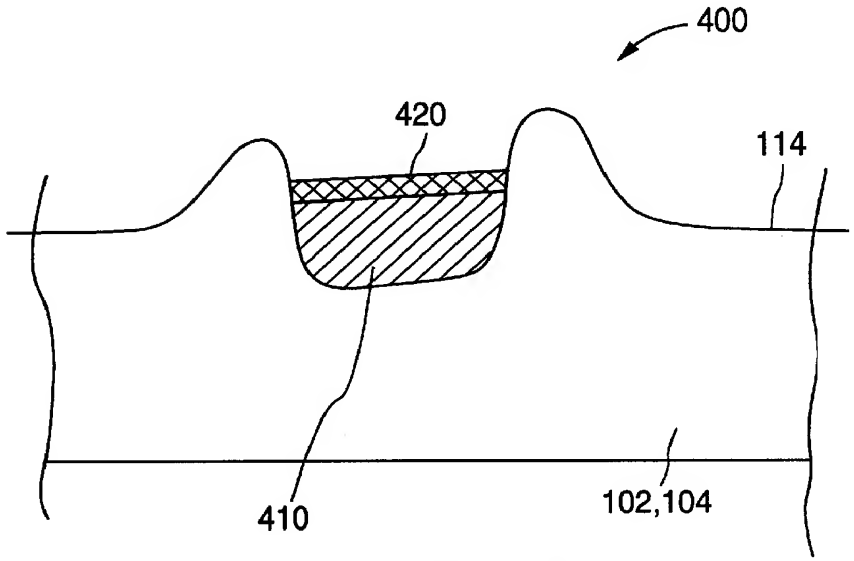


FIGURE 4A

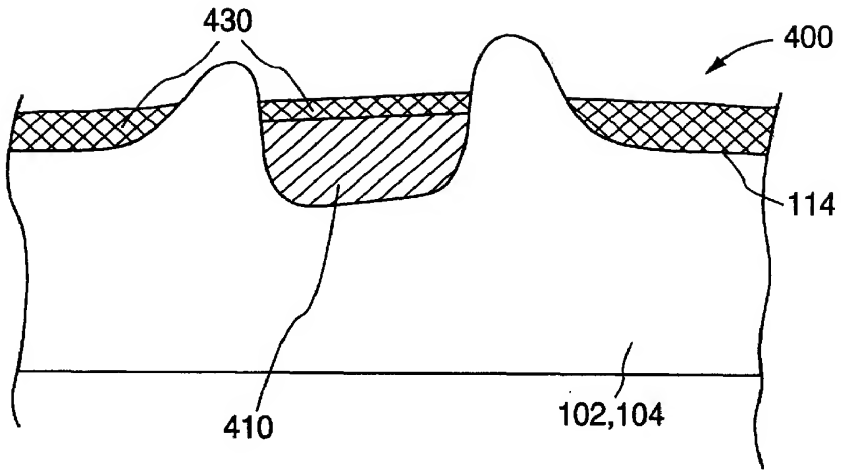


FIGURE 4B

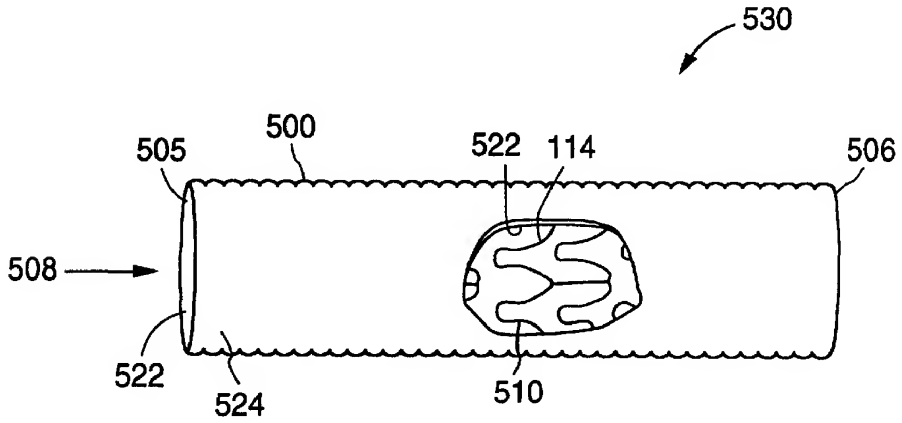


FIGURE 5A

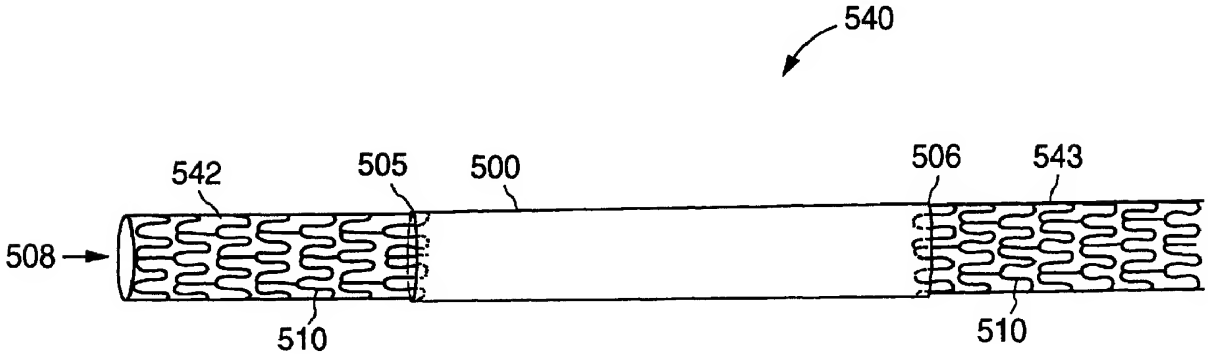


FIGURE 5B

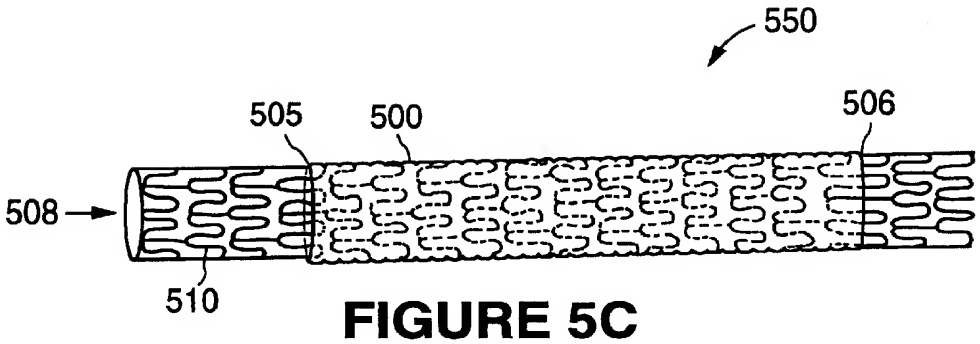


FIGURE 5C

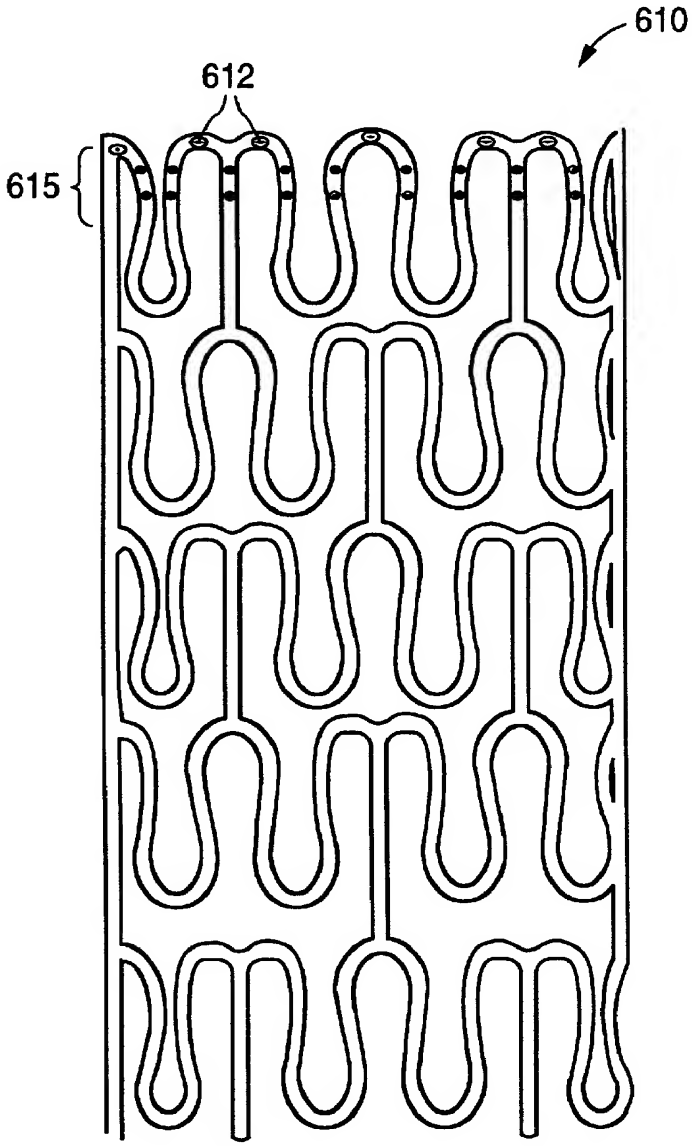


FIGURE 6A

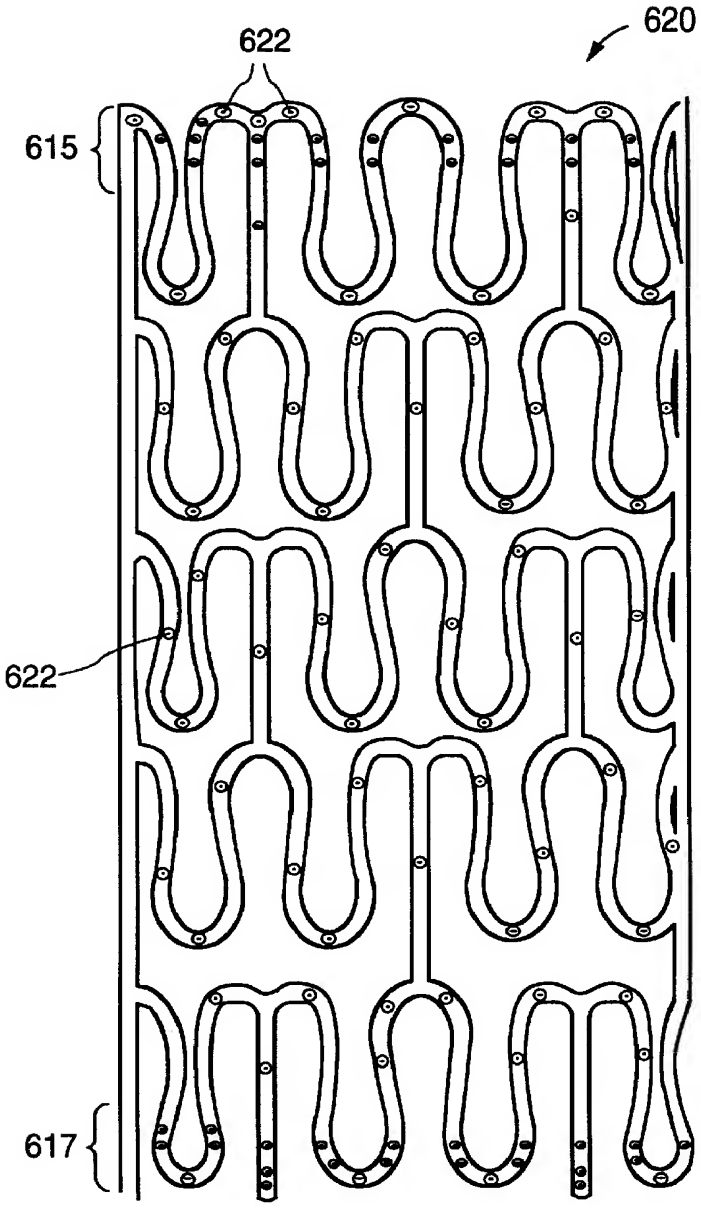


FIGURE 6B

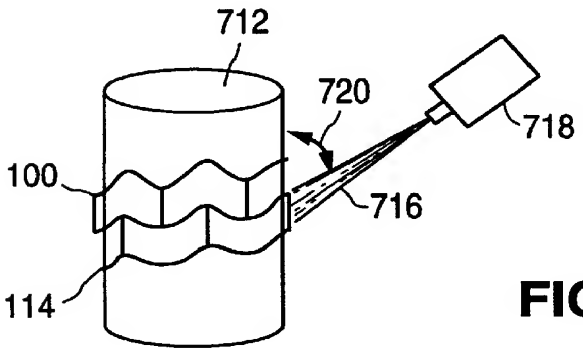


FIGURE 7

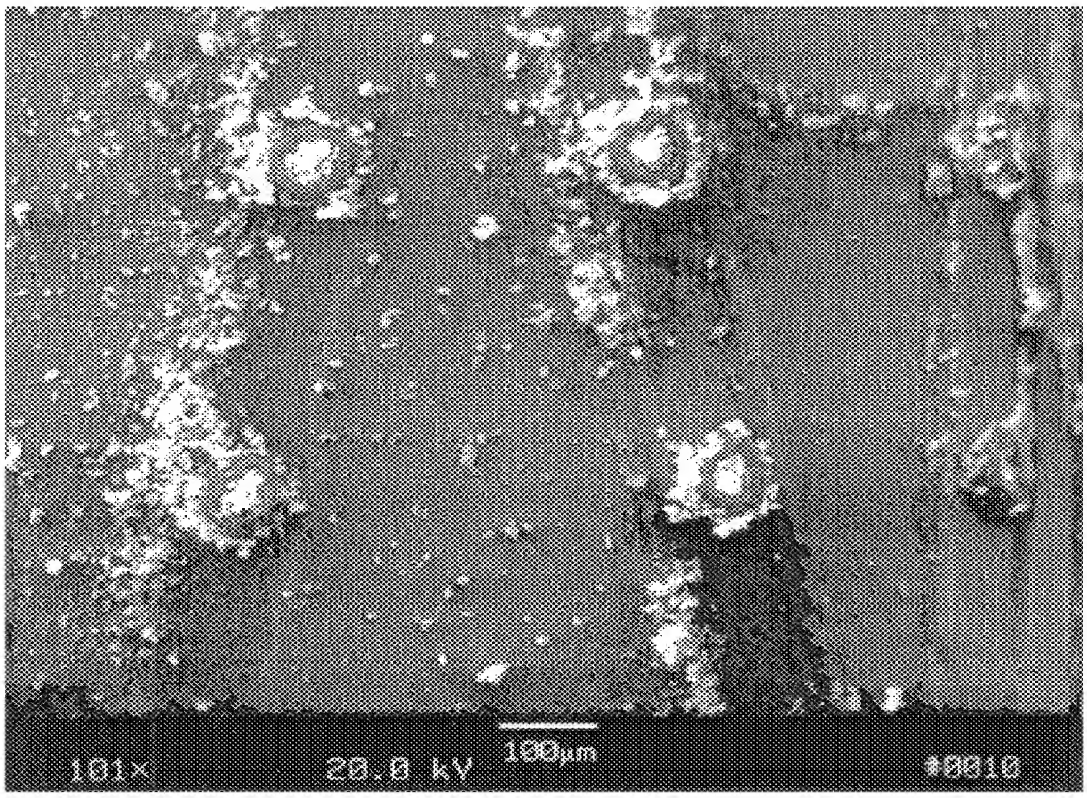


FIGURE 8A

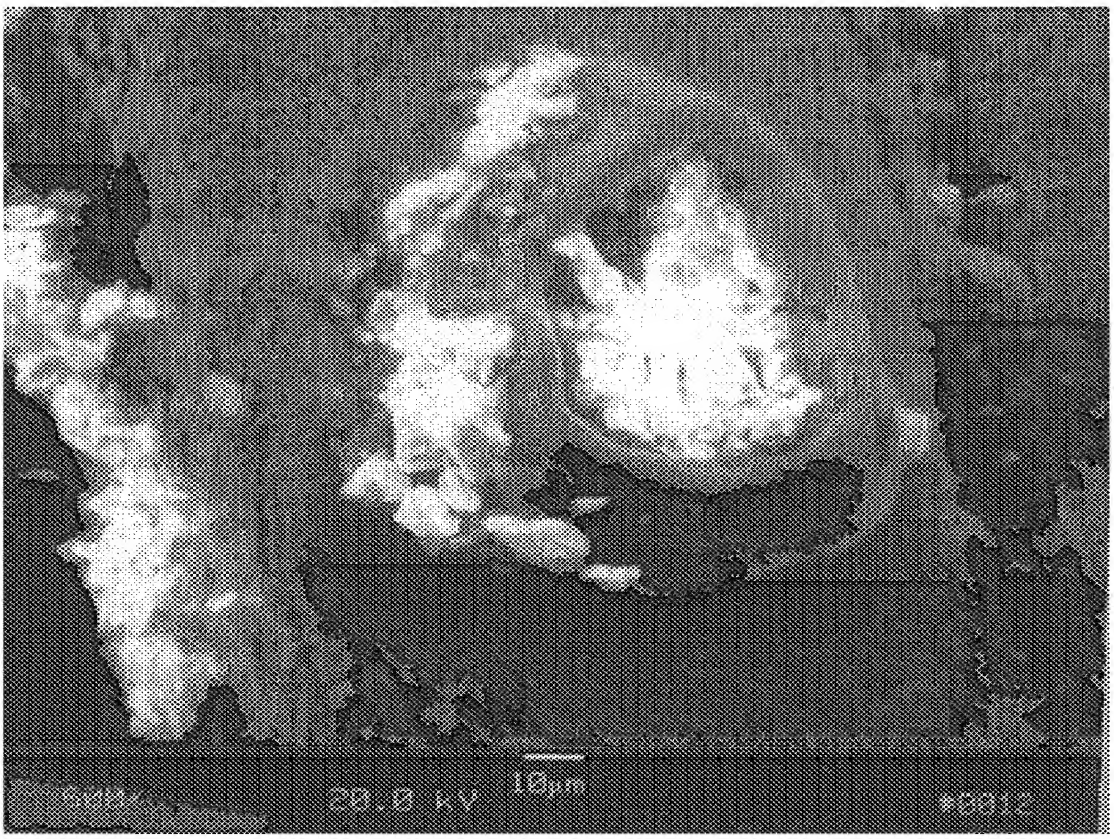


FIGURE 8B

IMPLANTABLE MEDICAL DEVICE HAVING PROTRUDING SURFACE STRUCTURES FOR DRUG DELIVERY AND COVER ATTACHMENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to medical devices, such as stents and covered stents. More particularly, the present invention is directed to a structure on the surface of the stent and a method for forming the structure.

2. Description of the Background

Certain implantable medical devices, such as stents and grafts, are implanted within blood vessels and other body passageways to treat disease conditions such as stenoses, occlusions, and aneurysms.

Stents are scaffoldings, usually cylindrical in shape that function to physically support, and, if desired, expand the wall of the passageway. Typically, a stent consists of two or more struts or wire support members connected together into a lattice-like or open weave frame.

Most stents are compressible for insertion through small cavities, and are delivered to the desired implantation site percutaneously via a catheter or similar transluminal device. Once at the treatment site, the compressed stent is expanded to fit within or expand the lumen of the passageway. Stents are typically either self-expanding or are expanded by inflating a balloon that is positioned inside the compressed stent at the end of the catheter. Intravascular stents are often deployed after coronary angioplasty procedures to reduce complications, such as the collapse of arterial lining, associated with the procedure.

In addition to providing physical support to passageways, stents are also used to carry therapeutic substances for local delivery of the substances to the damaged vasculature. For example, anticoagulants, antiplatelets, and cytostatic agents are substances commonly delivered from stents and are used to prevent thrombosis of the coronary lumen, to inhibit development of restenosis, and to reduce post-angioplasty proliferation of the vascular tissue, respectively. The therapeutic substances are typically either impregnated into the stent or carried in a polymer that coats the stent. The therapeutic substances are released from the stent or polymer once it has been implanted in the vessel.

A problem with delivering therapeutic substances from a stent is that, because of the limited size of the stent, the total amount of therapeutic substance that can be carried by the stent is limited. Furthermore, when the stent is implanted into a blood vessel, much of the released therapeutic substance enters the blood stream before it can benefit the damaged tissue. To improve the effectiveness of the therapeutic substances, it is desirable to maximize the amount of therapeutic substance that enters the local vascular tissue and minimize the amount that is swept away in the bloodstream.

The lattice-like structure of the stent leaves spaces defined by the struts that form the stent. These spaces can allow plaque from the lesion to fall through the stent and enter the blood stream during stent deployment. The spaces can also permit malignant tissue growth through the stent openings into the body passageway and can allow undesired contact between blood flowing through the blood vessel and damaged portions of the vessel intima. Covered stents, in which a polymeric material surrounds and is attached to the stent, have been proposed to alleviate the problems associated with stent openings.

Diseased vessels are also treated with grafts. Grafts are generally tubular in shape and are used to replace or create an anatomical passageway to provide a new conduit for fluid, e.g. blood. Grafts are often made from a portion of a vein, but can also be constructed from a synthetic material to form a synthetic graft. Like stents, synthetic grafts can be positioned percutaneously via a catheter, for instance, to be placed at the site of an aneurysm to prevent further dilation and possible rupture of the diseased vessel.

In certain instances, the graft material alone does not provide enough structural support for the graft, causing the graft to collapse and occlude or impede the flow of blood through the vessel. To counter this problem, a similar, even identical, structure to the covered stent, in which a stent is placed within the synthetic graft material, has been proposed to improve the structural strength of grafts. This structure is sometimes referred to as a synthetic stent graft. Stents are also placed at the ends of synthetic grafts to help secure the ends of the synthetic graft to vessel walls.

Examples in the patent literature of covered stents include U.S. Pat. No. 5,948,191 titled "Low profile, thermally set wrapped cover for a percutaneously deployed stent" issued to Solovay; U.S. Pat. No. 5,123,917 titled "Expandable intraluminal vascular graft" issued to Lee; U.S. Pat. No. 5,948,018 titled "Expandable supportive endoluminal grafts" issued to Dereume et al.; U.S. Pat. No. 5,282,824 titled "Percutaneous stent assembly" issued to Gianturco; U.S. Pat. No. 5,843,164 titled "Intraluminal stent for attaching a graft" issued to Franzen; and U.S. Pat. No. 6,010,530 titled "Self-expanding endoluminal prosthesis" issued to Goicoechea.

A problem with covered stents and synthetic stent grafts is keeping the stent covering attached to the stent. During expansion of the prosthesis, the covering pulls isometrically, causing the cover to shorten and possibly detach from the stent.

Currently, covers are attached to stents by stitching or gluing, or by wholly embedding the stent into the polymeric cover material. When stitches are used, the cover is typically punctured at the stitch site, leaving an opening and a weak place in the cover that may tear or rip when the covered stent is expanded. Using glue instead of stitches eliminates these problems, however, glue can be difficult to keep in place on the stent when attaching the cover material. Furthermore, in some cases, the glue itself does not provide a strong enough hold to keep the cover attached. When the stent is wholly embedded into the cover material, the covering is on both the inside and outside of the stent and may cause the profile of the covered stent to be larger than desired.

SUMMARY

In the embodiments of the present invention, protruding structures are provided for the surface of a stent or other implantable medical device. The protruding structures can be used with covered stents and synthetic stent grafts to engage and secure the cover, advantageously improving retention of the covering. The protruding structures can also be used to keep glue in place on the stent when attaching the covering. The protruding structures can also be used to deliver therapeutic substances from the stent directly to the lumen wall and advantageously minimize the amount of therapeutic substance swept away in the blood stream.

An exemplary protruding structure includes a depression region having a bottom surface that is fully or partially surrounded by a protruding lip. The depression region is approximately centrally located in the protruding structure

and the lip is higher than the bottom surface relative to the surface of the stent.

The protruding structure can have a variety of shapes, including a generally circular shape so that the protruding structure forms a crater, and an elongated shape so that the protruding structure forms a groove.

The bottom surface of the protruding structure can be above the surface of the stent or can be beneath the surface of the stent. In general, the distance between the bottom surface of the protruding structure and the stent surface is less than 80% of the distance between the inner and outer surfaces of the stent.

The protruding structures on the stent can contain one or more therapeutic substances. The therapeutic substances can be covered by a polymeric layer, which can reduce the release rate of the therapeutic substances from the stent for a delayed or sustained delivery.

A polymeric cover can be attached to a portion of the stent using the protruding structures, forming a covered stent. The protruding structures engage the cover. A glue can be added to the protruding structures to help secure the cover onto the stent. The cover can contain a therapeutic substance.

The cover can be shaped as a tube, having a first end and an opposing second end and a hollow bore extending longitudinally through the cover from the first to second end. The cover can concentrically enclose the outer surface of the stent. The cover can also be attached to two portions of the stent, one at each end of the cover, that include the protruding structures on their respective surfaces.

In one embodiment of the method within the present invention, the protruding structures can be made by directing a laser discharge at the surface of a stent to form a hole in the stent, and projecting a stream of pressurized grit onto the surface at and around the hole. The pressurized grit can be beads or sand, among other possibilities.

These and other embodiments and aspects of the present invention will be better understood in view of the drawings and the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a perspective view of an example of a stent in an expanded state.

FIG. **2**A is a perspective view of a portion of a stent strut with a crater on one of its surfaces.

FIG. **2**B is a cross-sectional side view of a portion of a stent strut with a crater that has a bottom surface recessed beneath the stent surface.

FIG. **2**C is a cross-sectional side view of a portion of a stent strut with a crater that has a bottom surface elevated above the stent surface.

FIG. **3**A is a perspective view of a portion of a stent strut with a protruding structure having an ovular shape.

FIG. **3**B is a perspective view of a portion of a stent strut with a protruding structure shaped as a groove.

FIG. **3**C is a side view of a portion of a stent strut with a groove such as that illustrated in FIG. **3**B in the center of the strut and running throughout the strut.

FIG. **3**D is a perspective view of a protruding structure having a lip that only partially surrounds the depression region.

FIGS. **4**A and **4**B are cross-sectional side views of protruding structures that contain a therapeutic substance or substances that are covered by a polymeric layer.

FIG. **5**A is a side view of a covered stent illustrating a stent inside of a cover.

FIG. **5**B is a side view of covered stent with the stent in two sections and attached to each end of a cover.

FIG. **5**C is a side view of a covered stent in which the stent extends beyond the ends of a cover.

FIG. **6**A is a side view of a stent that has protruding structures on only one end of the stent.

FIG. **6**B is a side view of a stent that has a higher density of protruding structures on both of the ends of the stent than in the central portion of the stent.

FIG. **7** is a schematic representation of the method of using a pressurized grit source in the process of forming protruding structures on the stent surface.

FIG. **8**A is a scanning electron micrograph photograph of a portion of a stent with protruding structures on the stent struts.

FIG. **8**B is a scanning electron micrograph photograph of a portion of a stent strut showing a protruding structure.

DETAILED DESCRIPTION

In the discussion below, examples of the present invention are provided in the context of stents and grafts. Artisans will appreciate, however, that the present invention also may be used in association with other types of implantable medical devices, such as an implantable disk, joint, or pacemaker, among other possibilities.

FIG. **1** illustrates an exemplary stent **100**. Stent **100** is a patterned cylindrical device that includes a plurality of radially expanding cylindrical struts **102** disposed generally coaxially and interconnected by connecting struts **104** that are disposed between and connect adjacent cylindrical struts **102**. Struts **102** and **104** can be any suitable thickness between the stent outer surface **114** and inner surface **112**. Typically thickness (T, illustrated in FIG. **2**A) is in the range of approximately 20 μm (0.001 inches) to 200 μm (0.008 inches). Struts **102** and **104** can also have any suitable width (W, illustrated in FIG. **2**A), typically in the range 100 μm (0.004 inches) to 1000 μm (0.04 inches). A specific choice of thickness and width depends on the application of the stent. These parameters will vary depending on, for example, the anatomy and size of the target lumen.

The stent may be made of any suitable biocompatible material such as a metallic material or an alloy, examples of which include, but are not limited to, stainless steel, "MP35N," "MP20N," elastinite (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The stent also may be made from bioabsorbable or biostable polymers.

Although stent **100** is illustratively shown in the configuration **100** of FIG. **1**, the stent **100** may be of virtually any configuration so long as stent **100** meets the needs of the treatment procedure and, if used as a covered stent, is capable of securely receiving a cover. Other configurations, such as helices, coils, braids, or the like may be utilized depending on the application for the prosthesis. For example, if the prosthesis is to be inserted percutaneously by use of a catheter, the stent will need to be capable of radially compressing and expanding, as discussed above.

In accordance with the various embodiments of the present invention, at least a portion of the outer surface **114**

of stent **100** contains protruding structures that have a depression region substantially surrounded by a lip. The lip extends above the plane of the stent surface **114** and above the depression region.

In one embodiment, the protruding structures have approximately circular shapes and are referred to herein as "craters". As illustrated by the exemplary crater **200** in FIG. **2**A, an approximately circular depression region **202**, located approximately in the center of crater **200**, is surrounded by a wall-like lip **204** that extends above the plane of the stent surface **114**. The lip **204** has an outer surface **206**, and an inner surface **208** that is within depression region **202**. The central depression region has a bottom surface **210**.

Dimensions that define the exemplary crater **200** are illustrated in FIGS. **2**B and **2**C, which are cross-sectional side views of craters taken along a line II illustrated in FIG. **2**A. Dimensions include the diameter **212** of the bottom surface **210**; the diameter **214** of the rim **213** of the lip **204**; and the diameter **216** of the total crater **200**. The height **218** of lip **204** is the distance above the stent surface plane **114** to the top of lip **204**. The depth **220** of the depression region **202** is the distance from top of the lip **204** to the bottom surface **210**. The depression area has a volume, defined by the volume encompassed by the bottom surface **210**, the inner surface **208** of lip **204**, and an imaginary top on the crater that is even with the top of the lip **204**.

The size of the crater is also defined by the circumference of the rim **213** of the lip **204**, the circumference of the bottom surface **210**, and the total circumference of the crater **200**, which is the circumference around the base **224** of the lip on the stent surface **112**, **114**. Note that the circumference of the bottom surface **210** may be different, typically smaller, than the circumference of the rim **213** of the lip **204**. The total circumference of the crater **200** is typically larger than both the circumference of the bottom surface **210** and the circumference of the rim **213**. The lip **204** also has a width **226**. Lip width **226** is typically larger at the base **224** of the lip **204** than at the rim **213**, although, in some embodiments, it may be constant over the entire lip **204**.

Bottom surface **210** of the depression region can be beneath the stent surface plane **114**, as illustrated in FIG. **2**B, above the stent surface plane, as illustrated in FIG. **2**C, or approximately even with the stent surface plane. If the bottom surface **210** of the depression region is beneath the stent surface plane, the recession depth **230** is typically less than 80% of the strut thickness so that the structural integrity of the strut is not compromised.

In other embodiments, the protruding structure can have a variety of shapes besides the generally circular shape illustrated for crater **200** in FIG. **2**A. For example, the protruding structure can be ovular, as illustrated by exemplary protruding structure **310** in FIG. **3**A. For such an ovular protruding structure, the size is defined by the length **314** and width **312** of the depression region, and the perimeters of the rim **213**, the bottom surface **210**, and the total protruding structure **310**. In one embodiment, the length **314** of protruding structure **310** is extended, and the protruding structure forms a groove, as illustrated by exemplary groove **320** in FIG. **3**B. In one embodiment, the groove **322** is in approximately the center of the stent strut **102**, **104**. The groove **322** can run along the length of the stent struts **102** and **104**, as illustrated in FIG. **3**C for a portion of a stent **330**. Additional variations of the protruding structures can be formed, for example, the lip may only partially surround the depression region, as illustrated by exemplary protruding structure **350** in FIG. **3**D.

The dimensions of the protruding structure depend on the intended application, and hence, dimension and design, of the stent. The largest diameter **216** (or width **312** if the protruding structure is non-circular) is limited by the width W of the stent strut into which the protruding structure is to be formed. Generally, the diameter **216** (or width **312**) is between 10% and 80% of the strut width W. The height of the protruding structure, for instance the lip height **218**, which is typically less than the strut thickness, will also depend on the design of the stent. For instance, if the stent is to be covered, the cover thickness will be a factor in determining desired lip height, as described below.

In one embodiment, the protruding structures, such as craters **200**, are located on the outer surface **114** of the stent and engage the lumen of the passageway when the stent is deployed, to help prevent the stent from slipping out of the treatment site.

A therapeutic substance or substances can be added to all or some of the protruding structures so that the therapeutic substance or substances are released from the stent when implanted in a vessel. The protruding lip will push into the lumen wall and will help to contain the therapeutic substance or substances to prevent loss of therapeutic substance to blood flowing through the vessel. This can advantageously increase the amount of therapeutic substance that is delivered directly to the tissue of the lumen wall.

FIGS. **4**A and **4**B illustrate a cross-sectional side views of a protruding structure **400** that contains the therapeutic substance or substances **410**. In one embodiment a top layer of a polymeric material is applied on top of the therapeutic substance or substances to control the release of the substance **410**. As illustrated in FIG. **4**A, the polymeric layer **420** may be only within protruding structure, or, as illustrated in FIG. **4**B, the polymeric layer **430** may cover the stent surface as well.

Polymeric materials that can be used for layer **420**, **430** are typically either bioabsorbable or biostable. A bioabsorbable polymer bio-degrades or breaks down in the body and is not present sufficiently long after implantation to cause an adverse local response. Bioabsorbable polymers are gradually absorbed or eliminated by the body by hydrolysis, metabolic process, bulk, or surface erosion. Examples of bioabsorbable, biodegradable materials include but are not limited to polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly (amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. Biomolecules such as heparin, fibrin, fibrinogen, cellulose, starch, and collagen are typically also suitable. Examples of biostable polymers include Parylene®, Parylast®, polyurethane (for example, segmented polyurethanes such as Biospan®), polyethylene, polyethylene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide.

In generally, the greater the total volume of depression region **202** on the stent, the greater the amount of therapeutic substance that can be carried by the stent. Therefore, a larger number of protruding structures having a greater depth **220** and greater bottom surface **210** area allows for more therapeutic substance to be carried by the stent. However, the structural integrity of the stent should not be compromised

by the protruding structures, and therefore limits the total volume of depression region **202** of the stent.

Therapeutic substances contained in the protruding structures can include, but are not limited to, antineoplastic, antimitotic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergenic substances as well as combinations thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g., Taxotere® from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.) Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g., Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g., Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, seratonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergenic agent is permirolast potassium. Other therapeutic substances or agents that may be used include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. In other examples, the therapeutic substance is a radioactive isotope for prosthesis usage in radiotherapeutic procedures. Examples of radioactive isotopes include, but are not limited to, phosphoric acid ($H_3P^{32}O_4$), palladium (Pd^{103}), cesium (Cs^{131}), and iodine (I^{125}). While the preventative and treatment properties of the foregoing therapeutic substances or agents are well-known to those of ordinary skill in the art, the substances or agents are provided by way of example and are not meant to be limiting. Other therapeutic substances are equally applicable for use with the protruding structures.

In one embodiment, the protruding structures (with or without a therapeutic substance therein) are used on a stent that is covered. The protruding structures engage and secure the cover by providing a mechanical hold for the cover, which prevents the cover from slipping or peeling off of the stent.

FIGS. **5A–5C** illustrate exemplary covered stents, also referred to as synthetic stent grafts. Cover **500** is attached to stent **510** and is typically shaped as a tubular sleeve having an open first end **505** and an open second end **506**. A central hollow bore **508** extends longitudinally through the cover **500**. Cover **500** has an inner surface **522** and an outer surface **524**.

Cover **500** is typically located on the outside of the stent **510**, as illustrated by exemplary covered stent **530** in FIG. **5A**, such that inner surface **522** of cover **500** is attached to the outer surface **114** of the stent **510**. In another embodiment, cover **500** may be on both sides of the stent **510**, for instance, the stent struts may be embedded into a polymeric material that forms the cover.

Cover **500** may encompass all or a portion of the stent **510**. In one embodiment, illustrated by exemplary covered stent **540** in FIG. **5B**, the cover **500** is attached at ends **505**, **506** to two stent sections **542**, **543**, one at each of the cover ends **505** and **506**, respectively. In this embodiment, the stent sections at each end of cover **500** can be used to secure the covered stent to the inside of a vessel wall, for instance when treating an aneurysm, such as an abdominal aortic aneurysm.

In another embodiment, illustrated by exemplary covered stent **550** in FIG. **5C**, the stent extends all the way through and beyond the ends of the cover, so that portions of the stent are exposed on each end of the cover. Various other combinations of cover (or covers) and stent sections can be used.

Stent **550** may be a single unit, as illustrated in FIGS. **5A** and **5C**, or may consist of independent sections, as illustrated in FIG. **5B**.

The protruding structures can be put onto the stent in varying locations depending on the design of the covered stent. For example, for the covered stent **540** illustrated in FIG. **5B**, the cover **500** is attached to only a portion, such as one of the ends of the stent sections **542**, **543**. In this instance the protruding structures are formed only on those places that will contact and secure the cover **500**, such as protruding structures **612** along end **615** of the stent **610** illustrated in FIG. **6A**.

The protruding structures can be formed on the stent surface in varying densities. Typically, the higher the number of protruding structures, the better the retention of the cover. However, too high a density of the protruding structures may compromise the structural integrity of the stent. The density of structures can also vary depending on the location of the structures on the strut. For example, the stent **620** illustrated in FIG. **6B** is for use with a covered stent, such as those illustrated in FIGS. **5A** and **5C**, in which the entire cover is attached to the stent. The protruding structures **622** can have a higher density at the ends **615** and **617** of the stent **620**, where a cover that surrounds the stent will be pulled and shortened the most as the stent expands. Protruding structures **622** on other portions of the stent may reduce the stress on the cover as it is pulled.

In one embodiment, a glue or adhesive is used in addition to the protruding structures to enhance the retention of the cover. The glue can be put into the depression region (**202**

of FIG. 2A), for instance, by using a syringe, before the cover **500** is put onto the stent **510**. The lip **204** will surround and contain the glue, making it less likely that the glue or adhesive will slip off of the stent when the cover is affixed, and protecting the glue from possible chemical and/or mechanical degradation due to blood once the covered stent is implanted. Glues that can be used should be biocompatible and include, but are not limited to, tetrafluoroethyleneperfluoropropylene copolymer (FEP), silicone, and polyurethanes.

The height of the protruding structures and the thickness of the cover depend on the design and application of the covered stent. Covers typically have a thickness in the range of 25 μm to 500 μm. In some applications, the height of the protruding structure is less than the cover thickness, so that the structures do not protrude above the cover. In other embodiments, the height is greater than the cover thickness, which may advantageously also allow the protruding structures to anchor the covered stent to the lumen wall. Typically, the protruding structures will indent and deform, but generally not puncture, the cover.

The cover can be preformed before being attached to the stent by methods such as molding, solvent casting, or weaving. The preformed cover can then be attached to the stent by mechanically pressing or crimping the cover onto the stent surface, which may also contain glue, as described above. The preformed cover can also be heat shrunk onto the stent for attachment.

In one embodiment, instead of attaching a preformed cover, the cover is formed directly on the stent. In one method the cover material is dissolved in a solvent or is in a malleable phase and is molded onto or around the stent and allowed to dry or harden to form the covered stent. Alternatively, cover material precursors are dissolved in solution and the solution molded onto the stent and then cross-reacted to form the cover.

The cover **500** can be made from any suitable, biocompatible material, including, but not limited to highly porous materials such as polymers of expanded polytetrafluoroethylene (ePTFE) and polyethylene terephthalate (PET). In an alternate embodiment, cover **500** is made from a less porous material, such as, but not limited to, polyurethanes, absorbable polymers, and combinations or variations thereof. Polyurethanes from which cover **500** may be made include, but are not limited to, Biomer, Biospan, and Elastion. Absorbable polymers from which cover **100** may be made include, but are not limited to, polycaprolactone (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polyanhydrides, polyorthoesters, polyphosphazenes, and components of extracellular matrix (ECM). Cover **500** can also be made from autologous fibrin. Teflon and Dacron, materials commonly used to make synthetic vascular grafts, can also be used to form cover **500**. Cover **500** may be made of one or more layers of one or more materials.

Cover **500** can also contain a therapeutic substance or substances that may be released from the cover after the covered stent has been implanted. Methods of impregnating a cover with therapeutic substances are well known. Therapeutic substances that can be impregnated in the cover include, but are not limited to, those listed above.

METHOD OF MAKING THE PROTRUDING STRUCTURES ON THE STENT

The lattice pattern of stent **100** can be cut from either a cylindrical tube of the stent material or from a flat piece of the stent material, which is then rolled and joined to form the stent. Methods of cutting the lattice pattern into the stent material include laser cutting and chemical etching, as described in U.S. Pat. No. 5,759,192 issued to Saunders and U.S. Pat. No. 5,421,955 issued to Lau, both patents incorporated herein by reference in their entirety.

The protruding structures can be formed before or after the stent lattice pattern is cut into the stent material. In one embodiment, protruding structures are formed on the stent by using a laser discharge to form holes into the stent in places where it is desired to have a protruding structure, and then directing a stream of pressurized grit at the stent in the area or areas where holes have been drilled.

It is believed that forming the hole with the laser leaves slag material around the outside edges of the drilled hole, which the pressurized grit then forms into the protruding structure shape. As the grit is directed at the stent surface, some of the stent material may be removed. However, some of the grit may be deposited in the central depression region of the hole, protecting that region from the pressurized grit and hence from removal of the stent material.

As an example, a pulsed ND:YAG (neodymium yttrium aluminum garnet) laser system (for example, model KLS 246 supplied by LASAG Industrial Lasers, Arlington, Ill.) that operates at 1064 nm, near infra-red spectrum, may be used to form holes in 316L stainless steel tubing that has a 1.78 mm (0.070 inch) outer diameter and a 152 μm (0.006 inch) thickness. The laser is pulsed at 1 Hz with a power level of 3.9 watts, which occurs at a voltage setting of 300 Volts. To determine the voltage setting necessary to achieve a given power level (3.9 W in this case), the pulse frequency is set at, for example, 1000 Hz and the voltage setting is adjusted while the power level is measured. Note that the power output for a given voltage setting varies with age of laser and other settings, such as aperture and frequency. The pulse length is 0.05 milliseconds. The feed rate, which is the rate the tubing moves across the laser beam, depends on the stent pattern, but can be nominally 12 inches per minute. This value changes with respect to the position and angle cuts made by the laser. The beam aperture will vary depending on the desired size of the protruding structure. In one example, the beam aperture can be 2.0 mm to create a protruding structure with a 1 μm diameter depression region. A 3.5 mm aperture will create a larger depression region. The intensity of the beam and dwell time can also be used to affect depression region size. Focus and nozzle height are set according to the size of the hypotube and the lamp intensity, which changes with use. In one embodiment, a focus of 9.38 and nozzle height of 0.368 inches (9.34 mm) is used. The beam expander is set to 7.0. The beam expander is used to change the angle the laser focuses onto the stent, which is used to adjust the focus of the laser beam at the stent surface. The beam expander allows the beam strength and beam diameter to be varied. As mentioned above, the beam diameter can also be varied by using the aperture. A low oxygen pressure, for example, 172 kPa, (26 PSI) is supplied when forming the holes. Of course, artisans will appreciate that the values given in the example (and throughout the description) are exemplary only, and not limiting.

To cut the stent pattern, the parameters of the laser system are typically altered. In one example, the stent is cut using a 1000 Hz pulse frequency and 0.075 millisecond pulse length. The power setting is 270 Volts to achieve 4.2 watts, and a 2.0 mm beam aperture in the beam path is used. The oxygen pressure has a high impact on cutting efficiency. For cutting the stent lattice pattern, high oxygen pressure, for example, 262 kPa (38 PSI), is used.

Often, cutting the lattice pattern into the stent, especially by laser, leaves scrap that must be removed, in a process known as descaling, to reveal the lattice pattern of the stent. Descaling is typically accomplished by ultrasonically cleaning the stent in heated acid, as described in U.S. Pat. No. 5,759,192.

After the holes are formed in the stent **100**, the stent lattice pattern cut, and, if necessary, the stent descaled, a process of directing a pressurized stream of grit material upon the stent **100** is performed. Examples of such processes include bead blasting and sand blasting. Bead blasting refers to the use of pressurized gas to project beads of a relatively uniform diameter at an object at a high velocity. The beads may be made of a variety of materials, such as latex, aluminum oxide, or silicon oxide. In sand blasting, the grit projected does not have as uniform a diameter as in bead blasting. Both bead blasting and sand blasting are techniques that are well known in the art.

FIG. **7** illustrates use of the pressurized grit source to form one embodiment of the stent, in which the protruding structures are formed on the outer surface **114** of the stent **100**. In FIG. **7**, the stent **100** is mounted onto a mandrel **712**. The stent is then rotated while the grit **716**, e.g. beads, is projected at the stent outer surface from the pressurized grit source **718**. The grit is projected at the stent at, for example, an approximately 30° angle **720** to the vertical axis of the stent, and is passed up and down over the outer surface **114** of the stent until the desired area of the stent, typically the area in which the holes have been formed, has been subjected to the stream. The visual appearance of the surface can be used to indicate that the blasted grit has been projected onto the area. The surface of the stent is smooth, shiny, and reflective before the bead or sand blasting process, but becomes dull, non-reflective, and of a darker color shade after the process. Subsequently, the stent is removed from the mandrel **712** and cleaned, for example by immersion and sonication in an isopropyl alcohol bath for approximately 20 minutes.

By way of example and not limitation, the grit can be beads having a diameter of between 1 μm and 50 μm. Pressures of, for example, 207 kPa (30 PSI) to, for example, 414 kPa (60 PSI) can be used to project the beads from a distance of, for example, approximately 3–10 cm from the stent. The grit source is passed very quickly, for example, in approximately 1–3 seconds, down and up over the stent in the areas of the stent that contain the holes.

In general, the shape of the protruding lip matches the shape of the hole formed with the laser. The shape of the protruding lip, for example the lip height, may be altered by changing, for instance, the hardness of the grit in relation to the hardness of the stent material, the speed the grit is projected, or the size and weight of the grit.

Scanning electron micrograph photographs of protruding structures that are craters and are formed by methods within the embodiments of the present invention are shown in FIGS. **8**A and **8**B. In these photographs, the stent has not yet been rinsed, for example in an alcohol bath as described above, and therefore beads from the bead blasting process (the white spheres) remain on the stent surface. In FIG. **8**A, the stent is only partially descaled. Six protruding structures are shown, 2 on each of 3 stent struts in the photograph. FIG. **8**B is a closer view of one of the protruding structures. The diameters **212**, **214**, and **216** of craters formed by this method typically are in the range of, for example, 20–100 μm. Depth **220** is typically in the range of, for example, 20–100 μm, and lip height **218** is typically in the range of, for example, 10–80 μm.

If desired, the stent surfaces that do not contain the protruding structures can be polished. For instance, it may be desirable to polish the inside surface **112** of the stent if the cover is to be attached to only the outside surface, as in, e.g., covered stent **530** of FIG. **5**A, because the inside surface will be in contact with blood components. Polishing is typically accomplished by use of an abrasive slurry or electropolishing. However, these polishing methods may remove the protruding structures formed on the surface. Therefore, a temporary protective coating can be applied to the portions of the surface to be protected (the portions containing the protruding structures) during the polishing process. For example, a poly vinyl alcohol (PVA) solution (80% by weight dissolved in hot water at 100° C.) can be applied to the inner surface with a syringe and allowed to air dry. The temporary coating can be removed by soaking the coated stent in water. Polishing can be done either before or after the stream of pressurized grit is used. If polishing is done before the pressurized grit is applied, the holes in the stent must also be protected from the polishing process by use of a temporary coating.

As discussed above, the protruding structures can be of any shape in addition to the generally circular shapes shown in FIGS. **2**A, **8**A, and **8**B. For instance, the protruding structures can have the exemplary shapes illustrated in FIGS. **3**A, **3**B, and **3**C. The sizes of the protruding structures can also vary. One method of varying the size and shape of the protruding structure is to mask the laser pulse to produce holes in the stent having a desired shape and size. For example, masking can be used to form holes with small diameters, in the range of, for example, 1–10 μm. The small diameter holes will result in small diameter protruding structures once the blasting with pressurized grit has been performed. In another method, useful for forming, for example, ovular or groove shaped protruding structures, the stent can be rotated and the laser moved across the strut surface for the desired distance to form the hole of the desired shape. Pressurized grit is then directed at the stent surface as described above to form the protruding structures.

Therapeutic substance may be added to the depression region of the protruding structure using any suitable method. In an exemplary method the therapeutic substance is mixed with a solvent, for example, 0.011 g of actinomycin D is mixed with 1.5 g of tetrahydrofuran. The implantable medical device with the protruding structures is then dipped in the therapeutic substance and solvent solution allowing the solution to fill the depression regions of the protruding structures. The implantable medical device is removed from the solution and allowed to dry. Any excess therapeutic substance not in the depression region is removed by blowing air at, for example, 620 kPa (90 PSI) toward the implantable medical device at a 90° angle, with the end of the air nozzle at, for example, approximately 10 cm from the surface of the device.

A polymer layer can then be added by dipping the device into a polymer and solvent solution, or, if desired, a polymer, solvent, and therapeutic substance solution. The solution is allowed to dry and, if desired, air can be blown at the device (e.g. 620 kPa, nozzle 10 cm from device, 90° angle) to clean excess solution off of the device.

While particular embodiments of the present invention have been shown and described, it will be clear to those of ordinary skill in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

What is claimed is:

1. An implantable medical device comprising:

a substrate having a first surface, said first surface having a plurality of protruding structures, wherein each of said protruding structures includes

a depression region having a bottom surface, said depression region approximately centrally located in said protruding structure; and

a lip surrounding at least a portion of said depression region, said lip having a height that extends above said bottom surface and said first surface.

2. The implantable medical device of claim 1, wherein said depression region and lip are substantially circular.

3. The implantable medical device claim 1, wherein said depression region and lip form a groove.

4. The implantable medical device of claim 1, wherein said substrate has a thickness defined by a distance between said first surface and an opposite second surface, said protruding structure has a depth defined by a distance between said bottom surface and said first surface, and said depth is less than 80% of said thickness.

5. The implantable medical device of claim 1, wherein said bottom surface is above said first surface.

6. The implantable medical device of claim 1, wherein said bottom surface is beneath said first surface.

7. The implantable medical device of claim 1 further comprising:

a cover overlying said first surface, wherein said protruding structures engage said cover.

8. The implantable medical device of claim 7 further comprising glue located in said depression region of at least some of said protruding structures.

9. The implantable medical device of claim 7, wherein said cover comprises a therapeutic substance.

10. The stent of claim 1, wherein said depression region contains one or more therapeutic substances.

11. The stent of claim 10, wherein said one or more therapeutic substances is covered by a polymeric layer.

12. A stent comprising:

a body having a generally cylindrical shape and an outer surface, wherein said outer surface includes a plurality of protruding structures, wherein said protruding structures include:

a depression region having a bottom surface, said depression region approximately centrally located in said protruding structure; and

a lip surrounding at least a portion of said depression region, said lip having a height that extends above said bottom surface and said outer surface.

13. The stent of claim 12 further comprising:

a cover overlying said outer surface, wherein said protruding structures engage said cover.

14. The stent of claim 13, wherein said cover has a first end and an opposing second end, wherein said stent comprises a first section and a second section, and wherein said first section is attached to said first end of said cover and said second section is attached to said second end of said cover.

15. The stent of claim 13, further comprising glue located in said depression region of at least some of said protruding structures.

16. The stent of claim 13, wherein said cover comprises a therapeutic substance.

17. The stent of claim 12, wherein said depression region and said lip are substantially circular.

18. The stent of claim 17, wherein said depression region contains one or more therapeutic substances.

19. The stent of claim 18, wherein said one or more therapeutic substances is covered by a polymeric layer.

20. The stent of claim 12, wherein said depression region and said lip form a groove.

21. The stent of claim 20, wherein said groove contains one or more therapeutic substances.

22. The stent of claim 21, wherein said one or more therapeutic substances is covered by a polymeric layer.

23. The stent of claim 12, wherein said body has a thickness defined by a distance between said outer surface and an opposite inner surface, said protruding structure has a depth defined by a distance between said bottom surface and said outer surface, and said depth is less than 80% of said thickness.

24. The stent of claim 12, wherein said bottom surface is above said outer surface.

25. The stent of claim 24, wherein said depression region contains one or more therapeutic substances.

26. The stent of claim 25, wherein said one or more therapeutic substances is covered by a polymeric layer.

27. The stent of claim 12, wherein said bottom surface is beneath said outer surface.

28. The stent of claim 27, wherein said depression region contains one or more therapeutic substances.

29. The stent of claim 28, wherein said one or more therapeutic substances is covered by a polymeric layer.

30. The stent of claim 12, wherein said depression region contains one or more therapeutic substances.

31. The stent of claim 30, wherein said one or more therapeutic substances is covered by a polymeric layer.

* * * * *

US006287628B1

(12) **United States Patent**
Hossainy et al.

(10) **Patent No.: US 6,287,628 B1**
(45) **Date of Patent: Sep. 11, 2001**

(54) **POROUS PROSTHESIS AND A METHOD OF DEPOSITING SUBSTANCES INTO THE PORES**

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(73) Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, CA (US)

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(52) **U.S. Cl.** **427/2.3**; 427/2.24; 427/2.25; 427/2.28; 427/230

(58) **Field of Search** 427/2.24, 2.25, 427/2.28, 2.3, 230, 346, 402; 604/266

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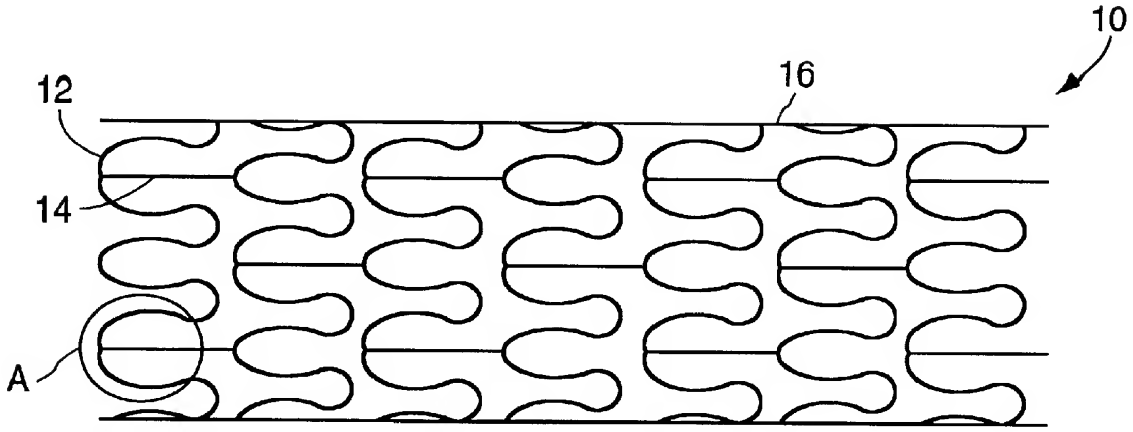
(57) **ABSTRACT**

A porous implantable prosthesis is loaded with a substance for subsequent application to biological tissues. A method according to loading the substance to the porous prosthesis is provided. A first fluid in combination with an added substance is applied to the porous prosthesis. During the application, the first fluid containing the substance is capable of penetrating into prosthesis pores. The first fluid is removed and a second fluid is applied to the prosthesis. The second fluid is not capable of significantly penetrating into the pores. Prior to the application of the second fluid, the prosthesis can be immersed in a third fluid and agitated via mechanical perturbation techniques so that any of the substance gathered on the surface of the body, after the application of the first fluid, is removed. The third fluid should not be capable of dissolving the substance.

36 Claims, 1 Drawing Sheet



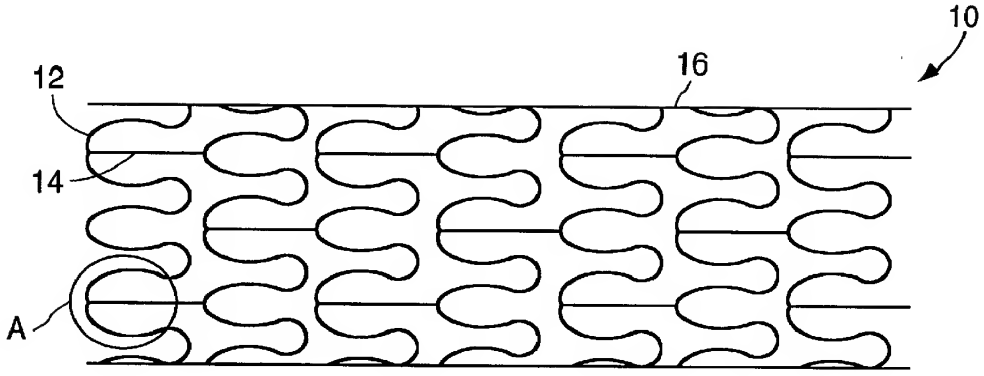


Fig. 1

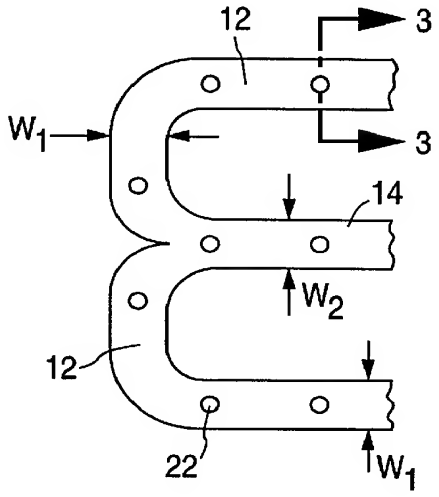


Fig. 2

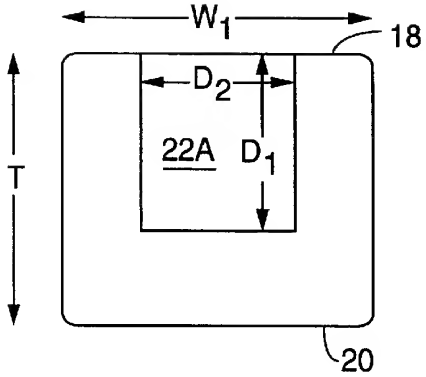


Fig. 3A

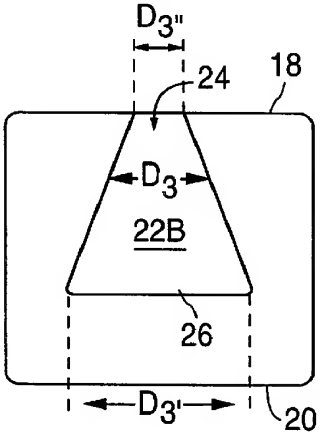


Fig. 3B

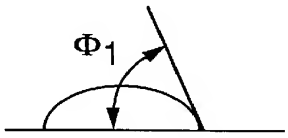


Fig. 4A

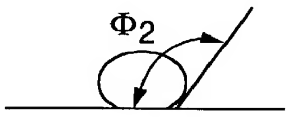


Fig. 4B

POROUS PROSTHESIS AND A METHOD OF DEPOSITING SUBSTANCES INTO THE PORES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to implantable devices, such as an expandable, intraluminal prosthesis commonly known as a stent. More particularly, this invention relates to a prosthesis having pores formed in its cylindrical body. Moreover, the present invention relates to a method of depositing substances, such as therapeutic substances, in the pores.

2. Description of the Background

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially press against the atherosclerotic plaque of the lesion to remodel the vessel wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, an intraluminal prosthesis, an example of which includes an expandable stent, is implanted in the lumen to maintain the vascular patency. Stents are scaffoldings, usually cylindrical or tubular in shape, functioning to physically hold open, and if desired, to expand the wall of the passageway. Typically stents are capable of being compressed for insertion through small cavities via small catheters, and then expanded to a larger diameter once at the desired location. Examples in patent literature disclosing stents which have been successfully applied in PTCA procedures include stents illustrated in U.S. Pat. Nos. 4,733,665 issued to Palmaz, 4,800,882 issued to Gianturco, and 4,886,062 issued to Wiktor.

In treating the damaged vasculature tissue and to further fight against thrombosis and restenosis, there is a need for administrating therapeutic substances to the treatment site. For example, anticoagulants, antiplatelets and cytostatic agents are commonly used to prevent thrombosis of the coronary lumen, to inhibit development of restenosis, and to reduce post-angioplasty proliferation of the vascular tissue, respectively. To provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a highly suitable method of treatment in that smaller levels of medication, as compared to systemic dosages, are concentrated at a specific site. Local delivery produces fewer side effects and achieves more effective results.

One commonly applied technique for the local delivery of the drugs is through the use of medicated stents. One proposed method of medicating stents is to seed the stent with endothelial cells (Dichek, D .A. et al. Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; Circulation 1989; 80: 1347–1353). Briefly, endothelial cells can be seeded onto stainless steel stents and grown until the stents are covered. The cells are therefore able to be delivered to the vascular wall to provide therapeutic proteins. Another proposed method of providing therapeutic substances to the vascular wall includes simple heparin-coated metallic stent, whereby a heparin coating is ionically or covalently bonded to the stent. Disadvantages associated with the aforementioned methods include significant loss of the therapeutic substance from the body of the stent during delivery and expansion of the stent and an absolute lack of control of the release rate of the therapeutic substance from the stent. Another proposed method involves the use of a polymeric carrier coated onto the body of the stent, as disclosed in U.S. Pat. Nos. 5,464,650 issued to Berg et al., 5,605,696 issued to Eury et al., 5,865,814 issued to Tuch, and 5,700,286 issued to Tartaglia et al. Obstacles often encountered with the use of a polymeric coating include difficulties in coating a complicated geometrical structure, poor adhesion of the polymeric coating to the surface of a stent, and biocompatibility of the polymer. Accordingly, it is desirable to be able to secure the therapeutic substance directly onto the body of the stent. Not withstanding the benefits gained by securing a therapeutic substance to the body of the stent, it is also desirable to be able to secure other substances to the body of the stent, such as radiopaque materials, used to assist a physician to guide and deploy the stent at the proper site of treatment.

SUMMARY OF THE INVENTION

In accordance with various aspects of the present invention, an implantable prosthesis, one example of which includes a stent, is provided that is capable of being loaded with substances. The prosthesis is defined by a cylindrical shaped body having a thickness. Depots or pores are formed on the body at preselected locations. The depots have a preselected depth and shape. The depth of the depots can be equal to about 10% to about 90% of the thickness. In one embodiment, the depots can have a cylindrical shape. In another embodiment, the shape can be generally conical. Substances such as therapeutic substances, polymeric material, polymeric material containing therapeutic substances, radioactive isotopes, and radiopaque material can be deposited into the depots.

Another aspect of the present invention is a method of loading a substance into the depots. The method is applicable not only to the above-described prosthesis, but to any type of porous prosthesis. A first fluid having a substance added therein is applied to a porous prosthesis. During the application, the first fluid containing the substance is capable of penetrating into the pores. The first fluid is removed, for example by evaporation, and a second fluid is applied to the prosthesis. During the application of the second fluid, the second fluid is not capable of significantly penetrate into the pores. The second fluid can have a contact angle greater than about 90°. Contact angle is defined as the angle at the tangent of the fluid phase that has taken an equilibrium shape on a solid surface. In one embodiment of the present invention, the second fluid rinses the substance from the surface of the body of the prosthesis. In another embodiment, a therapeutic substance and/or a polymer can be added to the second fluid to form a coating of a therapeutic substance and/or polymer onto the surface of the body of the prosthesis.

In accordance to another embodiment, prior to the application of the second fluid, the prosthesis can be immersed in a third fluid and agitated via mechanical perturbation tech-

niques. Accordingly, any of the substance gathered on the surface of the body after the application of the first fluid is removed. The third fluid should not be capable of dissolving the substance. The third fluid can have a contact angle above 90°.

BRIEF DESCRIPTION OF THE DRAWINGS

The features of the described embodiments are specifically set forth in the appended claims. However, embodiments relating to both structure and method of operation are best understood by referring to the following description and accompanying drawings, in which similar parts are identified by like reference numerals.

FIG. **1** is a side view of a conventional intraluminal prosthesis, the body of the prosthesis being defined by cylindrical elements engaged to one another by connecting elements;

FIG. **2** is an enlarged view of section A of FIG. **1**, illustrating a portion of the cylindrical elements and connecting elements;

FIG. **3**A is a cross sectional view of the cylindrical element, taken in the direction of the arrows and along the plane of line **3**—**3** of FIG. **2**, illustrating a depot formed in the body of the prosthesis in accordance to one embodiment of the present invention;

FIG. **3**B is a cross sectional view of the cylindrical element, taken in the direction of the arrows and along the plane of line **3**—**3** of FIG. **2**, illustrating a depot formed in the body of the prosthesis in accordance to another embodiment of the present invention;

FIG. **4**A illustrates a fluid on a solid surface having a contact angle Φ_1; and

FIG. **4**B illustrates a fluid on a solid surface having a contact angle Φ_2.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. **1** illustrates an implantable prosthesis **10**, one example of which includes a stent. Stents are scaffoldings, usually cylindrical or tubular in shape, that are inserted into an anatomical passageway and operate to physically hold open and, if desired, to expand the wall of a passageway. Stents are capable of being compressed for insertion through small cavities via balloon-catheters, positioned in a desired location, then expanded to a larger diameter.

In one example, illustrated in FIGS. **1** and **2**, stent **10** includes a plurality of rigid but resiliently flexible thread elements **12** that are arranged in a sinusoid-like configuration that is connected to form a continuous ring or cylinder. The plurality of cylindrical thread elements **12** are radially expandable, disposed coaxially, and interconnected by connecting elements **14** that are disposed between adjacent cylindrical thread elements **12**, leaving gaps or lateral openings between adjacent cylindrical thread elements **12**. Although the thread elements **12** are illustratively shown in the form of cylinders or rings connected axially-displaced in-parallel, other configurations, such as helices, coils, or braids, and other connections may be utilized. Thread elements **12** and connecting elements **14** define a tubular stent body **16** having a lumen contacting surface **18** and an inner surface **20** as shown in FIGS. **3**A and **3**B.

Thread elements **12** have any suitable width W_1, typically in a range of widths W_1 from about 0.002 inches to about 0.006 inches. A common width W_1 is about 0.003 inches. Connecting elements **14** have any suitable width W_2, typically in a ranges of widths W_2 from about 0.002 inches to about 0.008 inches. A common width W_2 is about 0.005 inches. Additionally, thread elements **12** have any suitable thickness T, typically a thickness T in a range from about 0.002 inches to about 0.008 inches. A common thickness T is about 0.005 inches. Connecting elements **14** have any suitable thickness, typically in a range from about 0.002 inches to about 0.008 inches. A common connecting element **14** thickness is about 0.005 inches. A specific choice of width and thickness depends on the anatomy and size of the target lumen. In other words, the size of the stent can vary according to the intended procedure, anatomy, and usage.

In one embodiment, thread elements **12** and connecting elements **14** are typically fabricated from a metallic material or an alloy such as stainless steel (e.g., 316L), "MP35N," "MP20N," tantalum, nickel-titanium alloy (commercially available as Nitinol™), platinum-iridium alloy, gold, magnesium, or combinations of alloys. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" has a nominal composition of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" has a nominal composition of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The aforementioned list is merely a useful list of materials and that other materials are proven to function effectively.

A single depot or pore **22** or plurality of depots or pores **22** are formed as a laser trench or laser trenches on body **16** of stent **10** by exposing surface **18** to an energy discharge from a laser, such as an excimer laser. Alternative methods of forming depots **22** include physical or chemical etching techniques. Techniques of laser fabrication or etching to form depots **22** are well-known to one of ordinary skill in the art. Depots **22** can be formed in virtually any stent structure and not merely the above-described structure. Depots **22** are used for carrying a variety of substances including but not limited to therapeutic substances, polymers impregnated with therapeutic substances, radioactive isotopes, and radiopaque .materials. The location of depots **22** vary according to the intended usage and application of stent **10**. Depots **22** are formed by a manufacturer at any preselected location and have any preselected depth, size, and geometrical configuration. In one example, depots **22** are evenly distributed through body **16** and have an equal volume so that the tissue in contact with stent **10** receives an equal distribution of a therapeutic substance. Depth D_1 of depots **22** typically is varied in proportion to the thickness T of body **16** as well as the clinical purpose and usage.

For a stent **10** that carries a therapeutic substance or a polymeric carrier impregnated with a therapeutic substance, a suitable depot or pore depth D_1 has a range from about 10% to about 90% of thickness T. Typically, a depth not greater than about 50% of thickness T is most suitable. The specific depth D_1 of depots **22** depends on the amount of therapeutic substance that is to be deposited in depots **22**. In an example of stent **10** that carries a radioactive isotope, depth D_1 is typically about 10% to about 80% of thickness T. A more specific suitable depth D_1 is not greater than about 30% of thickness T.

For a stent **10** that carries a radiopaque material, a suitable depot or pore depth D_1 has a range from about 10% to about 90% of thickness T. Typically, a depth not greater than about 65% is most suitable. A depth D_1 greater than about 65% of thickness T may compromise the structural integrity and mechanical functionality of stent **10**. However the upper limit of depth D_1 varies depending on the material characteristics such as the hardness of the body **16**.

Depots **22** may be formed in a variety of selected geometrical shapes. Referring to FIG. **3A**, a depot **22A** has a generally cylindrical shape. A diameter D_2 of cylindrical depot **22A** typically has a range from about 10% to about 90% of width W_1 or W_2, although the diameter D_2 is usually not greater than about 80% of width W_1 or W_2. The specific diameter D_2 depends on the application and purpose of depots **22**. The upper limit of diameter D_2 varies depending on the material characteristics such as the hardness of the body **16**.

An alternative example of a depot **22B**, illustrated in FIG. **3B**, is generally conical in shape. Conical shaped depot **22B** has an open end **24** and a closed end **26**. The open end **24** is the end that contacts a surface of a tissue. A diameter D_3 of conical shaped depot **22B** is shown to decrease from closed end **26** to open end **24**. The largest diameter D_3' at the closed end **26** of conical shaped depot **22B** has a range from about 10% to about 80% of width W_1 or W_2. Generally, the largest diameter D_3' is not greater than about 70% of width W_1 or W_2. The smallest diameter D_3" at the open end **24** of conical shaped depot **22B** has a range from about 5% to about 70% of width W_1 or W_2. Generally, the smallest diameter D_3" is not greater than about 60% of width W_1 or W_2. The reduced size of opening **24** of conical shaped depot **22B**, as compared to that of the cylindrical shaped depot **22A**, reduces the rate at which a therapeutic substance is released once the stent is implanted at the desired location of treatment. The depots **22** can have a variety of other geometrical shapes, such as elongated trenches (not illustrated).

The depth D_1 and diameters D_2 and D_3 of the individual depots **22** formed on body **16** of stent **10** can vary relative to one another. In one example, the manufacturer selectively controls the volume of depots **22** on different positions of body **16**, either selectively varying the volume or making the volume consistent throughout body **16**. For some applications, consistent depot **22** volume is important for delivery of a therapeutic substance to insure that the substance is evenly distributed throughout stent **10** and results in consistent application of the therapeutic substance to the tissues in contact with surface **18** of stent **10**.

A factor for determining the size, geometry, and concentration of depots **22** is the overall porosity of stent **10**. Porosity is the total volume of pores in body **16** of stent **10** divided by the total volume of structural material of stent **10**. Porosity determines the capacity of substance that can be loaded into stent **10** of predetermined dimensions. High porosity can adversely affect the structural integrity, strength, and elasticity of stent **10**. Consequently, stent design includes consideration of a tradeoff between strength, on one hand, and stent profile and stent load capacity on the other hand.

Substances are deposited into depots or pores **22** using several illustrative methods. The methods are applicable to the illustrative stent **10** described hereinbefore and also to any type of porous prosthesis. In some examples, the deposited substance is a therapeutic substance or agent such as antineoplastics, antiinflammatory substances, antiplatelets, anticoagulants, fribrinolytics, thrombin inhibitors, antimitotics, and antiproliferatives. Examples of antineoplastics include paclitaxel and docetaxel. Examples of antiplatelets, anticoagulants, fribrinolytics, and thrombin inhibitors include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, flurouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril® (available from Squibb), Cilazapril® (available from Hofman-LaRoche), or Lisinopril® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, Lovastatin® (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. While the listed therapeutic substances or agents are well known for preventative and therapeutic utility, the substances are listed by way of example and are not meant to be limiting. Other therapeutic substances which are currently available or that may be developed in the future are equally applicable. The treatment of patients using the above mentioned medicines is well-known to those of ordinary skill in the art.

In other embodiments, the therapeutic substance is a radioactive isotope for stent usage in radiotherapeutic procedures. Examples of radioactive isotopes include, but are not limited to, phosphoric acid ($H_3P^{32}O_4$), palladium (Pd^{103}), cesium (Cs^{131}), and iodine (I^{125}).

A therapeutic substance is added to a first fluid or solvent. The therapeutic substance is dispersed throughout the first solvent so that it is in a true solution, saturated or supersaturated with the solvent or suspended in fine particles in the first solvent. If the therapeutic substance is suspended in particles in the first solvent, the pore size and the diameter of the opening of the pores are to be sufficiently large in comparison to the size of the particles to facilitate loading and unloading of the stent. In one example, suitable pores have a pore size that is more than ten times the particle size of a suspended therapeutic substance and an opening diameter that is more than five times the diameter of the particle size.

The first solvent can be virtually any solvent that is compatible with the therapeutic substance. A suitable first solvent typically has a high capillary permeation. Capillary permeation or wetting is the movement of fluid on a solid substrate driven by interfacial energetics. Capillary permeation is quantitated by a contact angle, defined as the angle at the tangent of the first solvent droplet in fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation corresponds to a contact angle less than about 90°.

For example, FIG. **4A** illustrates a fluid having a high capillary permeation that corresponds to a fluid contact angle Φ_1 less than about 90°. FIG. **4B** illustrates a fluid having a low capillary permeation that corresponds to a fluid contact angle Φ_2 greater than about 90°. The first solvent can have a viscosity not greater than about ten centipoise. A high capillary permeation and a viscosity not greater than about ten centipoise allows the first solvent to penetrate into the pores of the prosthesis more quickly, eliminating a requirement to apply the first solvent to the prosthesis for a

prolonged period of time. The first solvent can be volatile, facilitating evaporation of the first solvent. Useful examples of some first solvent include, but are not limited to, acetone, ethanol, methanol, isopropanol, tetrahydrofuran, and ethyl acetate. The first solvent is applied to a porous prosthesis, for example by immersing or spraying the solvent in procedures that are well-known to one having ordinary skill in the art.

The first solvent is applied for a predetermined period of time, the specific time depending on the capillary permeation and viscosity of the first solvent, the volume of the pores, and the amount of substance to be deposited. Therapeutic parameters such as the concentration of the therapeutic substance in the solvent and dosages depend on the duration of local release, the cumulative amount of release, and desired rate of release. Correlations and interrelations between the therapeutic parameters are well-known to one having ordinary skill in the art and are simply calculated.

After applying the first solvent for a selected duration, the first solvent is removed from the prosthesis. In one example, the first solvent is removed by evaporation in ambient pressure, room temperature, and anhydrous atmosphere and/or by exposure to mild heat (e.g., 60° C.) under a vacuum condition. The prosthesis typically has a clustered or gross formation of a therapeutic substance gathered on the body surface. The cluster is generally removed by immersing the prosthesis in a second fluid and agitating the prosthesis via mechanical perturbation techniques, such as vortexing or vigorous shaking. The second fluid is a non-solvent so that the therapeutic substance does not significantly dissolve in the second fluid. The non-solvent can have a low capillary permeation or a contact angle greater than about 90° and a viscosity not less than about 0.5 centipoise so that the second fluid is not capable of significantly penetrating into the pores during the process of agitation. Examples of a second fluid include but are not limited to saturated hydrocarbons or alkanes, such as hexane, heptane, and octane.

The prosthesis is rinsed in a third fluid. The third fluid is typically a solvent to facilitate dissolution of the therapeutic substance. The third fluid generally has a low capillary permeation, corresponding to a contact angle greater than about 90°. The third fluid has a viscosity of not less than about 1.0 centipoise and is therefore incapable of significantly penetrating into the pores during the rinsing stage. The rinsing is conducted rapidly for example in a range from 1 second to about 15 seconds, the exact duration depending on the solubility of the therapeutic substance in the solvent. Extended duration of exposure of the third solvent to the prosthesis may lead to the penetration of the third solvent into the pores.

The rinsing step is repeated, if desired, until all traces of therapeutic substance are removed from the surface of the stent. The third fluid removes excess traces of therapeutic substance from the surface of the prosthesis body. Useful examples of third fluids include but are not limited to dimethylsulfoxide (DMSO), water, DMSO in an aqueous solution, glyme, and glycerol. The third fluid is removed from the prosthesis body using a technique such as evaporation in ambient pressure, room temperature and anhydrous atmosphere and/or by exposure to mild heat (e.g., 60° C.) under vacuum condition. The first, second, third fluids are selected to not adversely affect the characteristics and composition of the therapeutic substance.

In one embodiment, the third fluid can be highly volatile, for example having a boiling point of not greater than about 60° C. at 1 atm. Accordingly, the third fluid is capable of rapidly evaporating. Rapid evaporation of the third fluid causes the third fluid to be removed from the prosthesis prior to any significant penetration of the third fluid in the pores. A useful example of a highly volatile third fluid includes, but is not limited to, Freon (e.g., Xerosolv™).

Once loaded, the therapeutic substance remains in the pores until prosthesis deployment and expansion. The expanded prosthesis engages the wall of the anatomical passageway and the therapeutic substance disseminates from the porous cavities and is absorbed into the tissue of the walls of the passageway that are in contact with the prosthesis.

In some embodiments, a surface of the stent is coated with a therapeutic substance in addition to having a therapeutic substance deposited in the pores. A coating of therapeutic substance on the surface of the prosthesis is formed by adding the therapeutic substance to the third fluid rinse. The therapeutic substance is dispersed through the third fluid to form a true solution with the third solvent, rather than a dispersion of fine particles. The therapeutic substance is a substance that is capable of absorbing or attaching to the prosthesis surface. For example, highly suitable therapeutic substances for a stainless steel prosthesis include taxol and dexamethasone. Suitable substances for a Nitinol™ prosthesis include aspirin and heparin. The therapeutic substance added to the third fluid can be the same substance as the therapeutic substance deposited in the pores or a different substance. Rinsing with the third fluid is optionally prolonged or repeated to increase the thickness of the prosthesis therapeutic substance coating.

In another example, a polymeric coating is formed on the surface of the prosthesis, covering the pores containing deposited therapeutic substance. The polymeric coating forms a membrane that reduces the rate of release of a therapeutic substance from the pores. A polymeric material is added to the third fluid rinse to form a coating made from the polymeric material on the prosthesis surface.

The polymeric material, by example and not limitation, forms about 1% to about 3% by weight of the total weight of the solution. The polymeric material is most suitably bio-compatible, including polymers that are non-toxic, non-inflammatory, chemically inert, and substantially non-immunogenetic in the applied amounts. The polymer is typically bioabsorbable or biostable. A bioabsorbable polymer bio-degrades or breaks down in the body and is not present sufficiently long after implantation to cause an adverse local response. Bioabsorbable polymers are gradually absorbed or eliminated by the body by hydrolysis, metabolic process, bulk, or surface erosion. Examples of bioabsorbable, biodegradable materials include but are not limited to polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. Biomolecules such as heparin, fibrin, fibrinogen, cellulose, starch, and collagen are typically also suitable. Examples of biostable polymers include Parylene®, Parylast®, polyurethane (for example, segmented polyurethanes such as Biospan®, polyethylene, polyethlyene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide.

After the evaporation of the third solvent, a polymeric layer remains on the surface of the prosthesis and over the

pores. The polymeric coating is alternatively formed by other conventional methods such as plasma polymerization, the practice of which is well known to one of ordinary skill in the art.

In another example, the aforementioned polymeric coating is impregnated with a therapeutic substance that is added to the third fluid-polymer mixture. Concentration of the therapeutic substance depends on release parameters including the duration of local release, the cumulative amount of release, and the desired rate of release. The correlations and interrelations between the release parameters are well-known to those of ordinary skill in the art and easily calculated. The polymeric material, by example and not limitation, makes up from about 1% to about 3% by weight of the total weight of the solution. The therapeutic substance, by example and not limitation, typically makes up about 0.3% to about 1% of the total weight of the solution. Once the third solvent is evaporated, a polymeric coating impregnated with a therapeutic substance remains on the surface, covering the therapeutic substance-filled pores.

In another example, a polymeric material, such as any of the polymeric materials listed herein, is impregnated with a therapeutic substance and deposited into the pores. The polymeric material reduces the rate of release of the therapeutic substance from the pores. The method of application includes adding a therapeutic substance and a polymer to a first fluid or solvent. The therapeutic substance is dispersed throughout the first solvent to dissolve into a true solution, or is saturated or supersaturated with the solvent or suspended in fine particles in the first solvent. The polymeric material is also dispersed throughout the first solvent to form a true solution, or is suspended in fine particles in the first solvent. Saturation or supersaturation of the polymer is less suitable since the viscosity of the first solvent is raised beyond a desired limit.

If the therapeutic substance is suspended in the first solvent, the pore size and the diameter of the opening of the pores are to be sufficiently large in comparison to the size of the particles to facilitate loading and unloading of the stent. In one example, suitable pores have a pore size that is more than ten times the particle size of a suspended therapeutic substance and an opening diameter that is more than five times the diameter of the particle size.

The first solvent is selected from among solvents that are compatible with the polymer and therapeutic substance. A first solvent having a high capillary permeation or a contact angle not higher than about 90° improves performance. The first solvent can have a viscosity not higher than about ten centipoise. The first solvent can be volatile to facilitate evaportation. Useful examples of a first solvent include, but are not limited to, acetone, ethanol, methanol, isopropanol, tetrahydrofuran, and ethyl acetate. The first solvent is applied to a porous prosthesis, by for example, immersing or spraying. The first solvent is applied for a predetermined time period, the specific time depending ono the capillary permeation and viscosity of the first solvent, volume of the pores, and the amount of substance to be deposited. Therapeutic parameters such as the concentration of the therapeutic substance and the specific polymer depend on the duration of the local release, the cumulative amount of release, and the rate of release is desired. Correlations and interrelations between the therapeutic parameters are well-known to those having ordinary skill in the art and are easily determined.

After a selected time duration, the first solvent is removed from the prosthesis by a technique such as evaporation in ambient pressure, room temperature, and anhydrous atmosphere and/or by exposure to mild heat (e.g., 60° C.) under vacuum condition. The prosthesis typically has a cluster of polymeric material and therapeutic substance formed on the body surface. The cluster is removed by immersing the prosthesis in a second fluid and agitating the prosthesis via mechanical perturbation techniques, such as vortexing or vigorous shaking. The second fluid is a non-solvent so that the therapeutic substance and the polymer are not capable of dissolution in the second fluid. The non-solvent generally has a low capillary permeation, corresponding to a contact angle greater than about 90° and a viscosity not less than 0.5 centipoise so that the second fluid is not capable of significantly penetrating into the pores during the process of agitation. Examples of the second fluid include but are not limited to saturated hydrocarbons or alkanes, such as hexane, heptane, and octane.

The prosthesis is rinsed in a third fluid subsequent to the application of the first solvent or the agitation of the prosthesis. The third fluid typically has a low capillary permeation, corresponding to a contact angle greater than about 90°. The third fluid has a viscosity of not less than 1.0 centipoise. The third fluid is not capable of significantly penetrating into the pores during the rising stage. In one embodiment, the third fluid is capable of significantly dissolving both the therapeutic substance and the polymeric material. Rinsing is conducted rapidly, for example for a duration in a range from 1 second to about 15 seconds. The specific duration depends on the solubility of the therapeutic substance and the polymeric material characteristics. The rinsing is repeated, if desired, until all traces of therapeutic substance and polymeric material are removed from the stent surface.

In an alternative embodiment, the third fluid is capable of significantly dissolving the therapeutic substance but not the polymeric material. As a result, traces of therapeutic substance are removed from the surface of the prosthesis, leaving a polymeric coating covering the surface of the prosthesis including the pores. The polymeric coating serves as an additional rate-reducing membrane. Useful examples of third fluid include but are not limited to DMSO, water, DMSO in an aqueous solution, and glycerol. The third fluid can be removed from the body of the prosthesis using a technique such as evaporation in ambient pressure, room temperature and anhydrous atmosphere and/or by exposure to mild heat (e.g., 60° C.) under vacuum condition. The first, second, third fluids, alone or in conjunction with the polymeric material should not adversely affect the characteristics and composition of the therapeutic substance.

In another example, a polymeric material, such as a material capable of swell-loading or post-loading, can be deposited into the pores. Swell-loading occurs when a polymeric carrier is soaked with a therapeutic substance/solvent solution. The polymer swells, receiving the therapeutic substance in the polymer matrix. Once the solvent is removed, the polymer collapses and is impregnated with the therapeutic substance. Examples of polymeric material that are susceptible to swell-loading include thermoplastic polymers such as polyurethanes, polylactic acid, and polyglycolic acid, and non-thermoplastic polymers such as polyethyleneglycol, polyvinyl alcohol, polyacrylamide, and tecophilic polymers. The method of depositing a polymeric material into the pores is generally similar to the above-described methods with an addition of a curing step for the non-thermoplastic polymers subsequent to the rinsing step. One of ordinary skill in the art of polymer fabrication understands how to cure a non-thermoplastic polymer.

In another example, a radiopaque substance such as gold is deposited into the pores. The process of depositing radioactive isotopes is generally similar to the methods described above with a radiopaque substance dispersed and suspended in fine particles through a first fluid. The first fluid can have a high capillary permeation or a contact angle not higher than about 90°. The first fluid has a viscosity not higher than about ten centipoise and can be volatile, ensuring that the first fluid evaporates more readily and easily. Useful examples of first fluids include acetone, ethanol, methanol, isopropanol, tetrahydrofuran, and ethyl acetate.

The first fluid is applied to a porous prosthesis for a predetermined period of time, typically about 30 minutes. After application, the first solvent is removed from the prosthesis using a technique such as evaporation in ambient pressure, room temperature, and anhydrous atmosphere and/or by exposure to mild heat (for example, 60° C.) under vacuum condition. The prosthesis may have a gross formation of radiopaque substance gathered on the prosthesis body surface. The radiopaque formation can be removed by immersing the prosthesis in a second fluid and agitating the prosthesis via mechanical perturbation techniques, such as vortexing or vigorous shaking. The second fluid can have a low capillary permeation or a contact angle greater than about 90° and a viscosity not less than about 0.5 centipoise so that the second fluid is not capable of significantly penetrating into the pores during the process of agitation. Examples of the second fluid include but are not limited to saturated hydrocarbons or alkanes, such as hexane, heptane, and octane.

The prosthesis is rinsed in a third fluid subsequent to the application of the first fluid or the agitation of the prosthesis. The third fluid has a low capillary permeation or a contact angle greater than about 90°, and has a viscosity not less than about 1.0 centipoise so that the third fluid is not capable of significantly penetrating into the pores during the rinsing stage. The rinsing is conducted rapidly, for example in a range from 1 second to about 15 seconds, since an extended exposure duration may result in penetration of the third fluid into the pores. Suitable materials for the third fluid include DMSO, water, glyme and glycerol. Rinsing is repeated, if desired, until all traces of radiopaque substance are removed from the surface of the stent. The third fluid is removed from the body of the prosthesis using a technique such as evaporation in ambient pressure, room temperature and anhydrous atmosphere or by exposure to mild heat (e.g., 60° C.) under vacuum condition. Sintering of the radiopaque material deposited in the pores is performed to bond particles of the radiopaque material without melting the particles. Appropriate pressure and temperature of radiopaque material sintering is specific to the particular material in a manner well known to one having ordinary skill in the art.

Several examples illustrate various methods for depositing substances such as therapeutic substances on a stent. The examples illustrate but do not limit the possible techniques for depositing substances.

EXAMPLE 1

Trapidil is dissolved in ethanol by conventional methods. Trapidil makes up about 15% by weight of the total weight of the solution. A stent having a porous surface is immersed in the solution for 30 minutes. The stent is removed and mounted on a mandrel at ambient pressure, room temperature, and anhydrous atmosphere for approximately 30 minutes, until the ethanol is evaporated. The stent is submerged in hexane, followed by mechanical perturbation in a vortex apparatus for about 15 seconds. The stent is removed from the non-solvent and rinsed with water for about 5 seconds. The stent is dried at ambient pressure, room temperature, and anhydrous atmosphere.

EXAMPLE 2

Trapidil is dissolved in ethanol by conventional methods. Trapidil makes up about 20% by weight of the total weight of the solution. A stent having a porous surface is immersed in the solution for 20 minutes. The stent is removed and mounted on a mandrel at ambient pressure, room temperature, and anhydrous atmosphere for approximately 30 minutes, until the ethanol is evaporated. The stent is submerged in heptane, followed by mechanical perturbation in vortex apparatus for 45 seconds. The stent is removed from the non-solvent and rinsed with dimethylsulfoxide (DMSO) for about 5 seconds. After rinsing, the mandrel is placed in ambient pressure, room temperature, and anhydrous atmosphere for approximately 2 hours, until the DMSO is evaporated.

EXAMPLE 3

Trapidil is dissolved in ethanol by conventional methods. Trapidil makes up about 25% by weight of the total weight of the solution. A stent having a porous surface is immersed in the solution for 20 minutes. The stent is removed and mounted on a mandrel at ambient pressure, room temperature, and anhydrous atmosphere for approximately 30 minutes, until the ethanol is evaporated. The stent is submerged in heptane, followed by mechanical perturbation in vortex apparatus for about 60. The stent is removed from the non-solvent and rinsed with a dimethylsulfoxide (DMSO) aqueous solution (having a 1:1 DMSO-water ratio) for about 5 seconds. After rinsing, the mandrel is placed in ambient pressure, room temperature, and anhydrous atmosphere for approximately 2 hours. Next, the prosthesis is placed in an oven under vacuum condition and at a temperature of about 60° C. for 24 hours, until all of the DMSO and water evaporated.

EXAMPLE 4

Trapidil is dissolved in ethanol by conventional methods. Trapidil makes up about 25% by weight of the total weight of the solution. A stent having a porous surface is immersed in the solution for 30 minutes. The stent is removed and mounted on a mandrel at ambient pressure, room temperature, and anhydrous conditions for approximately 30 minutes, until the ethanol is evaporated. The stent is submerged in heptane, followed by mechanical perturbation in a vortex apparatus for about 45 seconds. The stent is removed from the non-solvent and rinsed, for about 10 seconds, with solution of ethylene vinyl alcohol and DMSO, the ethylene vinyl alcohol constituting about 1% by weight of the total weight of the solution. The mandrel is placed in ambient pressure, room temperature, and anhydrous condition for approximately 2 hours. The stent is placed in a oven under vacuum condition and at a temperature of about 60° C. for 24 hours, until all of the DMSO is evaporated. A polymeric coating remains on the surface of the stent.

EXAMPLE 5

Trapidil is dissolved in ethanol by conventional methods. Trapidil makes up about 20% by weight of the total weight of the solution. A stent having a porous surface is immersed in the solution for 40 minutes. The stent is removed and

mounted on a mandrel at ambient pressure, room temperature, and anhydrous conditions for approximately 30 minutes, until the ethanol is evaporated. The stent is submerged in heptane, followed by mechanical perturbation in a vortex apparatus for about 30 seconds. The stent is removed from the non-solvent and rinsed, for about 10 seconds, with a solution containing ethylene vinyl alcohol, trapidil, and DMSO. The ethylene vinyl alcohol constitutes about 1% by weight and the trapidil constitutes about 0.33% by weight of the total weight of the solution. The mandrel is placed in ambient pressure, room temperature, and anhydrous condition for approximately 2 hours. The stent is placed in a oven under vacuum condition and at a temperature of about 60° C. for 24 hours, until all of the DMSO is evaporated. A polymeric coating having a trapidil impregnated therein remains on the stent.

EXAMPLE 6

Trapidil was dissolved in ethanol by conventional methods. Trapidil was used to make 40% by weight of the total weight of the solution. A stent having a porous surface was mounted on a mandrel and dipped in the 40% solution for 40 seconds. The stent was removed from the other end and dried at ambient pressure, room temperature, and anhydrous conditions for about 30 minutes, until the ethanol was evaporated. The stent was mounted on a mandrel again and rinsed in a heparin (DuraFlo™)/ Trapidil solution for 3 seconds. The solution constituted 0.6% by weight of Heparin and 0.6% by weight of Trapidil. The solvent used was Freon (Xerosolv) and n-Propanol in the ratio of 5:1 by volume. The stent was placed in a humidity controlled chamber at room temperature for 12 hours until all of the Freon and n-Propanol solvent system evaporated. A DuraFlo coating having Trapidil impregnated therein remained on the stent surface and inside the pores.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of the invention.

What is claimed is:

1. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid penetrates into said pores;

removing said first fluid from said prosthesis;

applying a second fluid to said prosthesis to remove said substance from said surface of said prosthesis, wherein said second fluid has a contact angle greater than about 90° so as to prevent said second fluid from significantly penetrating into said pores to remove said substance out from said pores during the application of said second fluid; and

removing said second fluid from said prosthesis, wherein said substance is deposited into said pores.

2. The method according to claim **1**, wherein said acts of removing said first fluid and said second fluid comprise allowing said first fluid and said second fluid to evaporate from said prosthesis.

3. The method according to claim **1**, additionally comprising prior to said act of applying said second fluid:

immersing said prosthesis in a third fluid, wherein said substance does not significantly dissolve in said third fluid;

agitating said prosthesis in said third fluid to significantly remove said substance from said surface of said prosthesis, wherein said substance remains in said pores; and

removing said prosthesis from said third fluid.

4. The method according to claim **3**, wherein said third fluid has a contact angle greater than about 90°.

5. The method according to claim **1**, wherein said substance is a first therapeutic substance.

6. The method according to claim **5**, additionally comprising, prior to said act of applying said second fluid:

immersing said prosthesis in a third fluid, wherein said first therapeutic substance does not significantly dissolve in said third fluid;

agitating said prosthesis in said third fluid to significantly remove said first therapeutic substance from said surface of said prosthesis, wherein said first therapeutic substance remains in said pores; and

removing said prosthesis from said third fluid.

7. The method according to claim **6**, wherein said third fluid has a contact angle greater than about 90°.

8. The method according to claim **5**, wherein said second fluid comprises a second therapeutic substance added thereto, such that after said act of removing said second fluid from said prosthesis, a coating of said second therapeutic substance remains on said surface of said prosthesis.

9. The method according to claim **8**, wherein said second therapeutic substance is the same as the first therapeutic substance.

10. The method according to claim **8**, wherein said second therapeutic substance is different than said first therapeutic substance.

11. The method according to claim **1**, wherein said second fluid comprises a polymeric material added thereto, such that after said act of removing said second fluid from said prosthesis, a coating of said polymeric material remains on said surface of said prosthesis.

12. The method according to claim **1**, wherein said second fluid comprises a combination of a polymeric material and a therapeutic substance added thereto, such that after said act of removing said second fluid from said prosthesis, a coating of said polymeric material containing said therapeutic substance remains of said surface of said prosthesis.

13. The method according to claim **1**, wherein said substance includes a polymeric material.

14. The method according to claim **13**, wherein said polymeric material significantly dissolves when in contact with said second fluid.

15. The method according to claim **13**, additionally comprising, prior to said act of applying said second fluid:

immersing said prosthesis in a third fluid, wherein said polymeric material does not significantly dissolve in said third fluid;

agitating said prosthesis in said third fluid to significantly remove said polymeric material from said surface of said prosthesis, wherein said polymeric material remains in said pores; and

removing said prosthesis from said third fluid.

16. The method according to claim **15**, wherein said third fluid has a contact angle greater than about 90°.

17. The method according to claim **13**, wherein said polymeric material is a non-thermoplastic polymer and the method additionally comprises the act of curing said non-thermoplastic polymer deposited in said pores.

18. The method according to claim 1, wherein said substance includes a polymeric material and a therapeutic substance.

19. The method according to claim 18, additionally comprising, prior to said act of applying said second fluid:

immersing said prosthesis in a third fluid, wherein said polymeric material and said therapeutic substance do not significantly dissolve in said third fluid;

agitating said prosthesis in said third fluid to significantly remove said polymeric material and said therapeutic substance from said surface of said prosthesis, wherein said polymeric material containing said therapeutic substance remains in said pores; and

removing said prosthesis from said third fluid.

20. The method according to claim 19, wherein said third fluid has a contact angle greater than about 90°.

21. The method according to claim 1, wherein said substance is a radioactive isotope.

22. The method according to claim 21, additionally comprising prior to said act of applying said second fluid:

immersing said prosthesis in a third fluid;

agitating said prosthesis in said third fluid to significantly remove said radioactive isotope from said surface of said prosthesis; and

removing said prosthesis from said third fluid.

23. The method according to claim 22, wherein said third fluid has a contact angle greater than about 90°.

24. The method according to claim 1, wherein said substance is a radiopaque material.

25. The method according to claim 24, additionally comprising, subsequent to said act of removing said second fluid, sintering said radiopaque material deposited in said pores.

26. The method according to claim 24, additionallt comprising prior to said act of applying said second fluid:

immersing and prosthesis in a third fluid;

agitating said prosthesis in said third fluid to significantly remove said radiopaque material from said surface of said prosthesis; and

removing said prosthesis from said third fluid.

27. The method according to claim 26, wherein said third fluid has a contact angle greater than about 90°.

28. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid penetrates into said pores;

removing said first fluid from said prosthesis;

applying a second fluid to said prosthesis, wherein during said act of applying said second fluid, said second fluid does not significantly penetrate into said pores; and

removing said second fluid from said prosthesis, wherein said substance is deposited into said pores, and

wherein said substance significantly dissolves when in contact with said second fluid.

29. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid penetrates into said pores;

removing said first fluid from said prosthesis;

applying a second fluid to said prosthesis, wherein during said act of applying said second fluid, said second fluid does not significantly penetrate into said pores; and

removing said second fluid from said prosthesis, wherein said substance is deposited into said pores,

wherein said substance is a therapeutic substance, and

wherein said therapeutic substance significantly dissolves when in contact with said second fluid.

30. The method according to claim 29, wherein said second fluid has a contact angle greater than about 90°.

31. The method according to claim 29, wherein said second fluid has a boiling point not greater than about 60° C. at 1 atm.

32. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid penetrates into said pores;

removing said first fluid from said prosthesis;

applying a second fluid to said prosthesis, wherein during said act of applying said second fluid, said second fluid does not significantly penetrate into said pores; and

removing said second fluid from said prosthesis, wherein said substance is deposited into said pores,

wherein said substance includes a polymeric material and a therapeutic substance, and

wherein said polymeric material and said therapeutic substance dissolve when in contact with said second fluid such that any of said polymeric material and said therapeutic substance disposed on said surface of said prosthesis are significantly removed.

33. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid penetrates into said pores;

removing said first fluid from said prosthesis;

applying a second fluid to said prosthesis, wherein during said act of applying said second fluid, said second fluid does not significantly penetrate into said pores; and

removing said second fluid from said prosthesis, wherein said substance is deposited into said pores,

wherein said substance includes a polymeric material and a therapeutic substance, and

wherein said therapeutic substance dissolves when in contact with said second fluid, wherein after said act of removing said second fluid a coating made from said polymeric material remains on said surface of said prosthesis and covers said pores.

34. The method according to claim 33, wherein said second fluid has a contact angle greater than about 90°.

35. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid and said substance penetrate into said pores;

allowing said first fluid to evaporate;

applying a second fluid to said prosthesis to remove said substance from said surface of said prosthesis, wherein said second fluid has a boiling point of not greater than about 60° C. at 1 atm; and

allowing said second fluid to evaporate, wherein said substance is deposited into said pores.

36. A method of loading a substance into pores of an implantable prosthesis:

providing a prosthesis having a surface and pores formed in said surface;

applying a first fluid including a substance to said prosthesis, wherein during said act of applying, said first fluid and said substance penetrate into said pores;

allowing said first fluid to evaporate;

applying a second fluid to said prosthesis to remove said substance from said surface of said prosthesis, wherein said second fluid has a viscosity not less than about 1.0 centipoise at room temperature; and

allowing said second fluid to evaporate, wherein said substance is deposited into said pores.

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